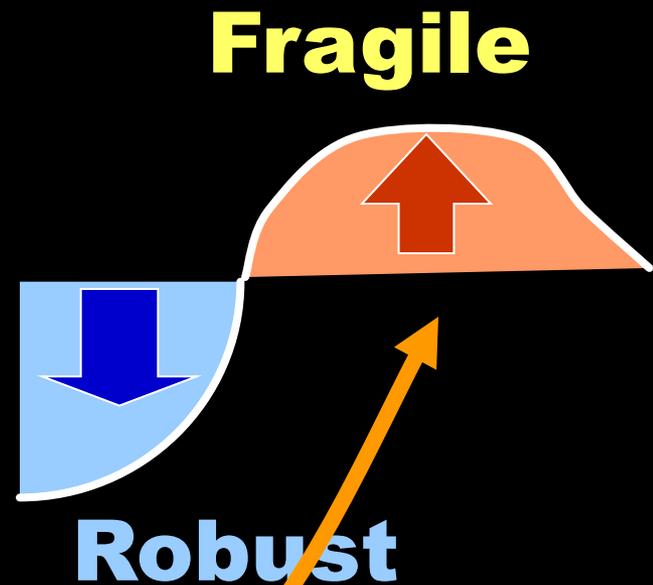


[a system] can have
[a property] *robust* for
[a set of perturbations]

Yet be *fragile for*

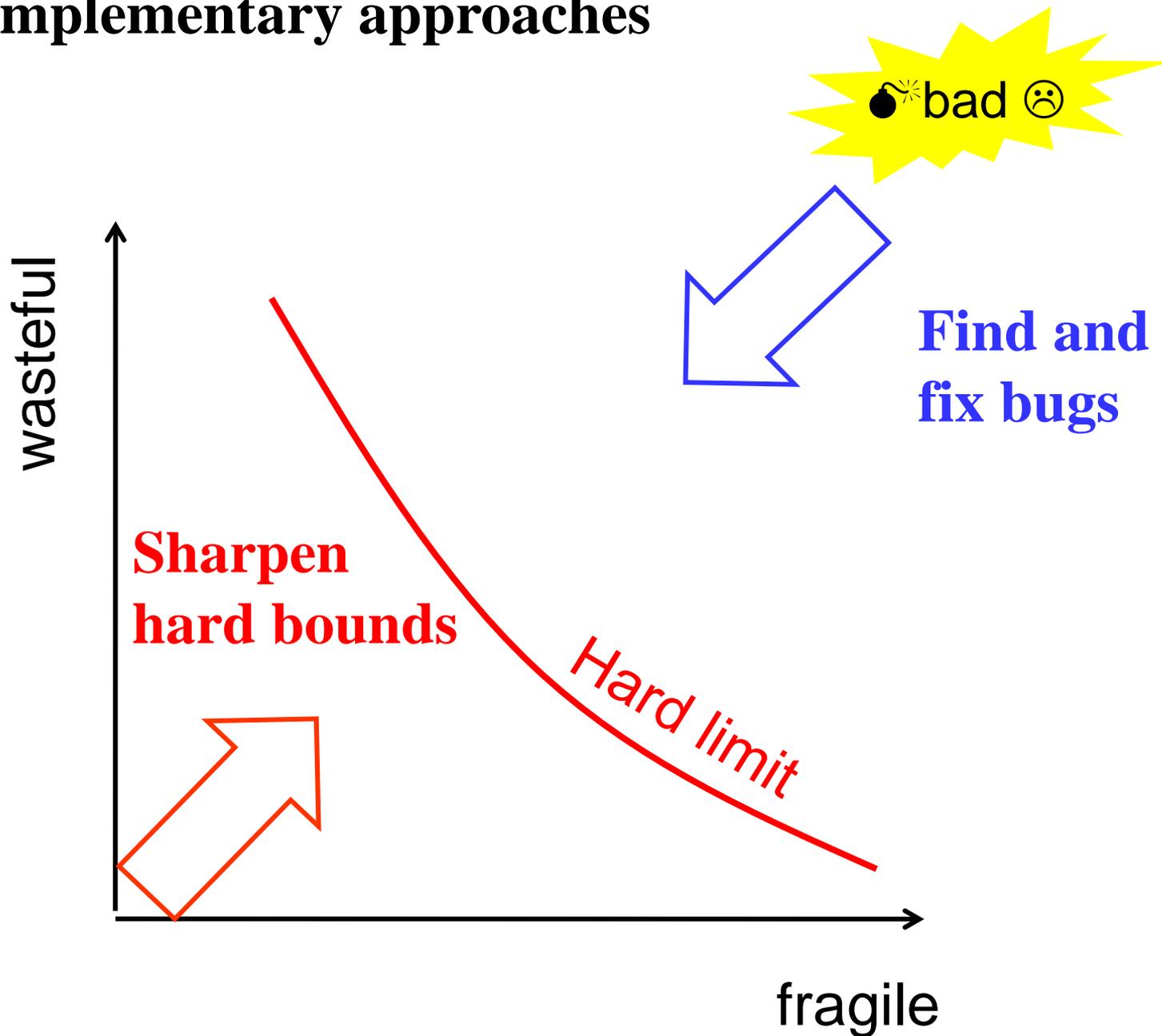
[a different property]

Or [a different perturbation]



Robust yet fragile = fragile robustness

Complementary approaches

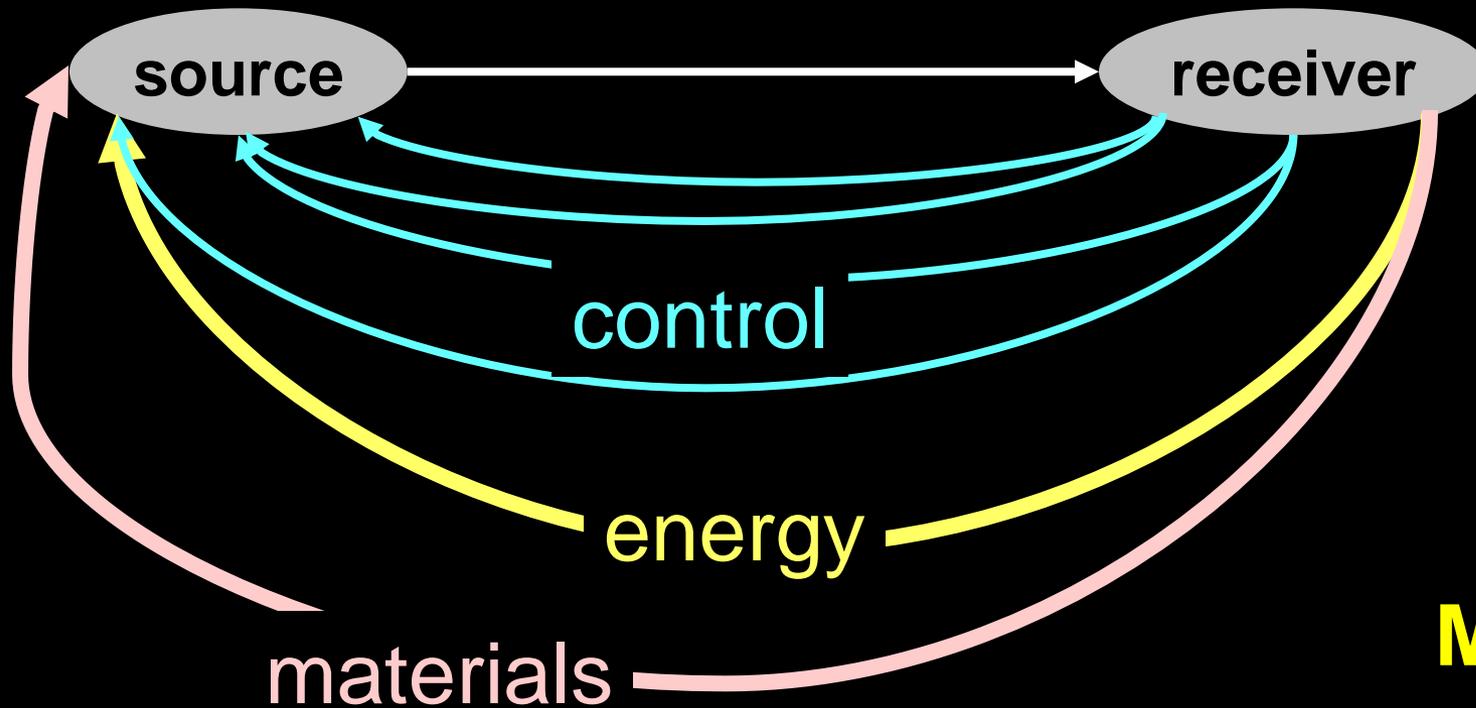


signaling
gene expression
metabolism
lineage

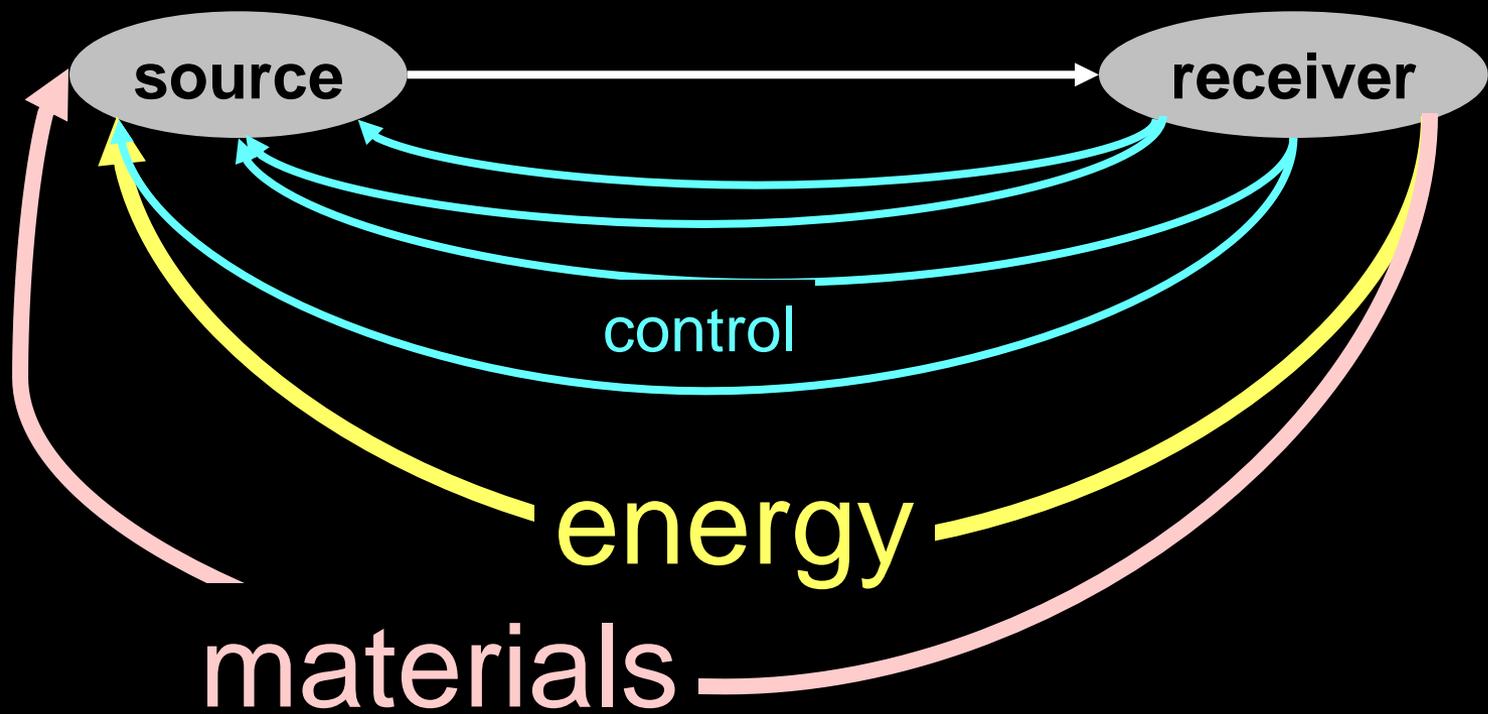


**Biological
pathways**

signaling
gene expression
metabolism
lineage

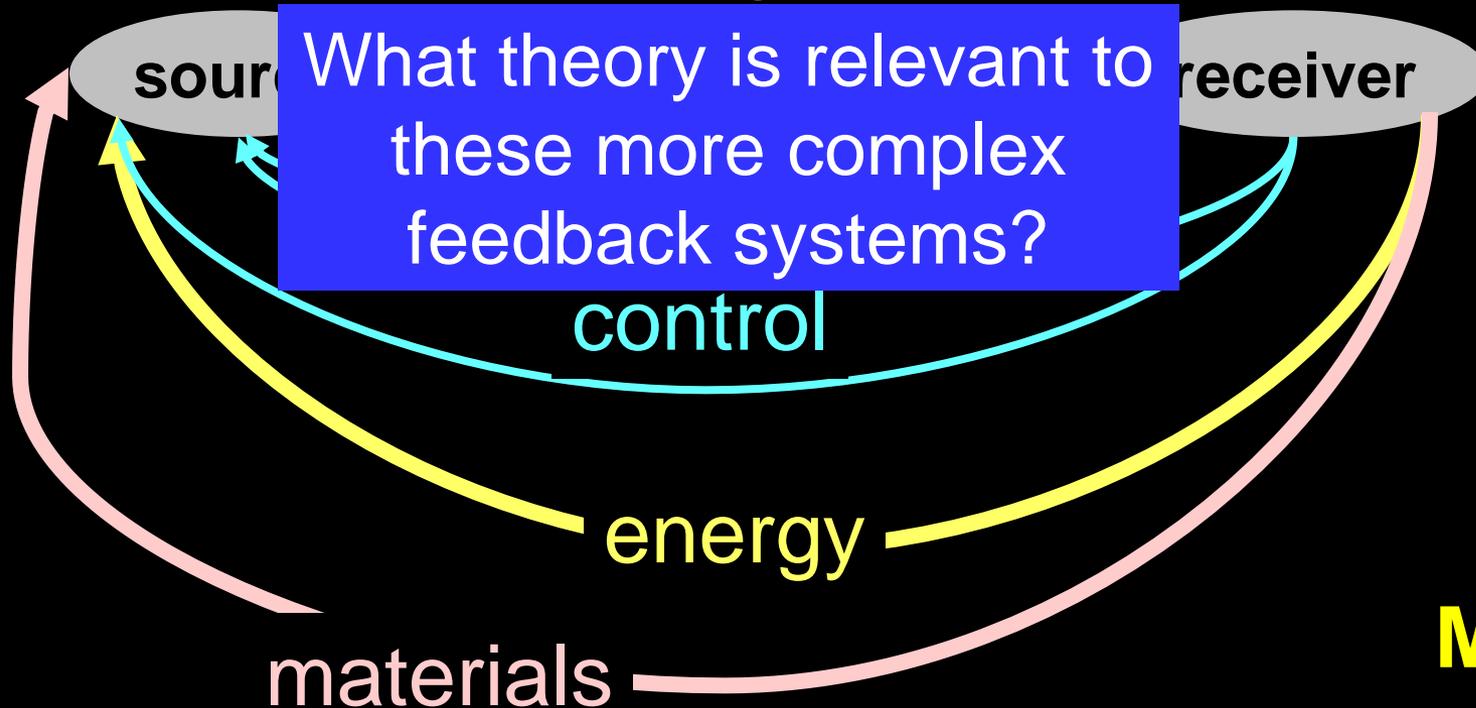


**More
complex
feedback**



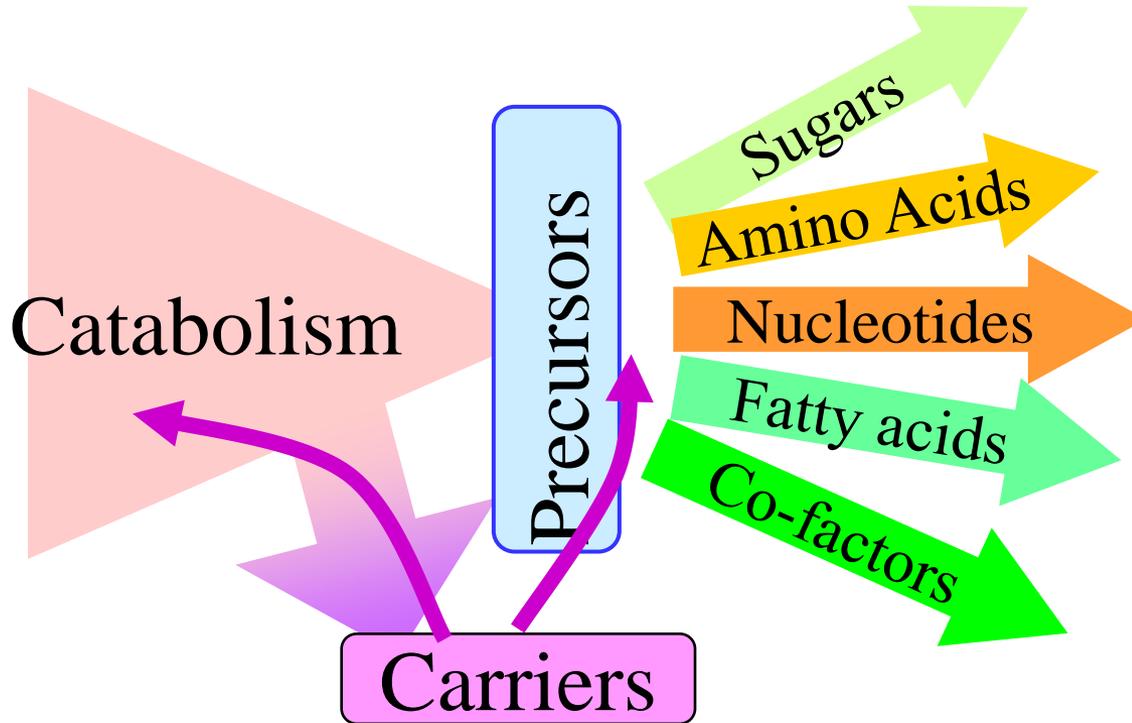
Autocatalytic feedback

signaling
gene expression
metabolism
lineage



**More
complex
feedback**

Inside every cell

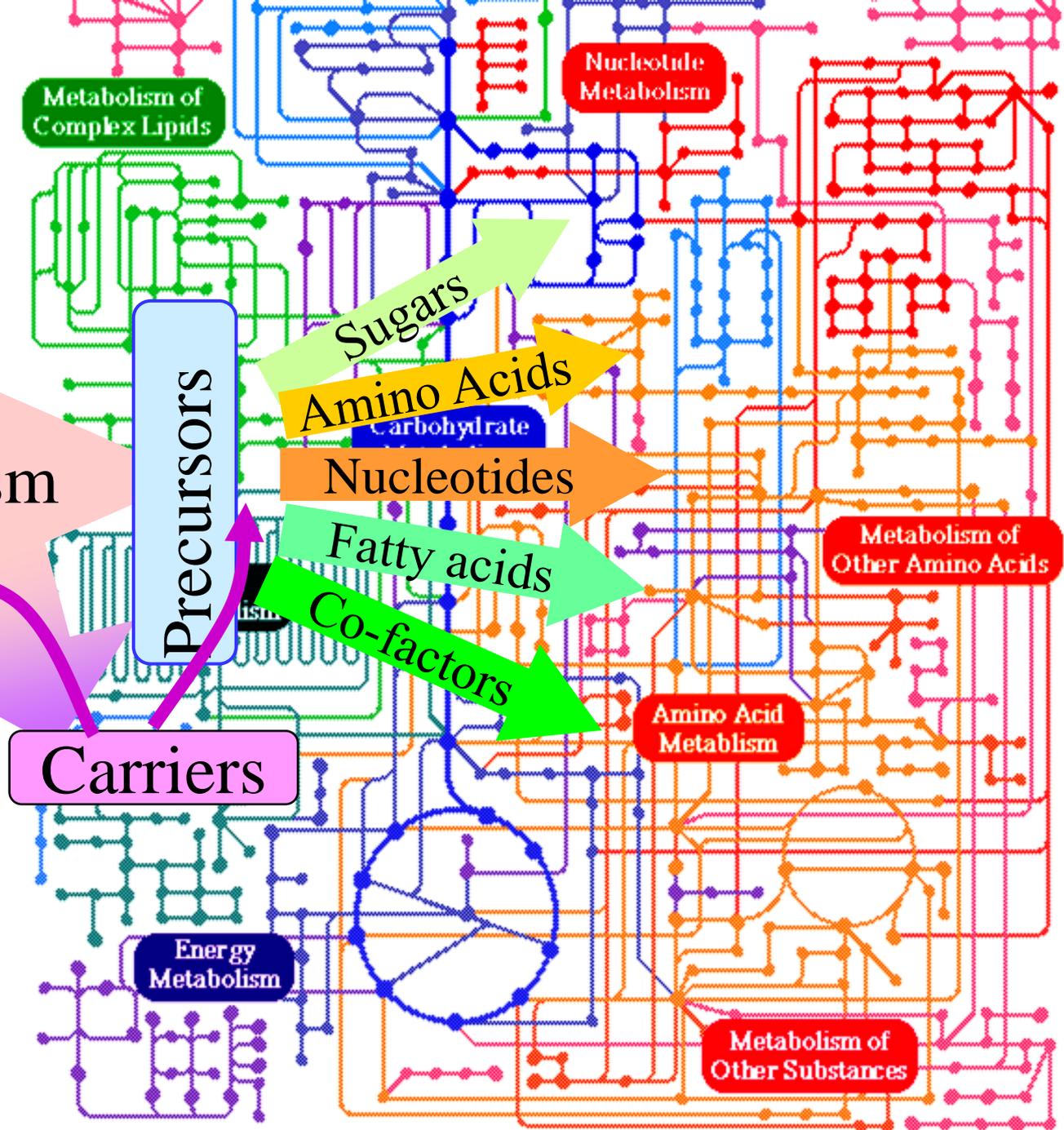


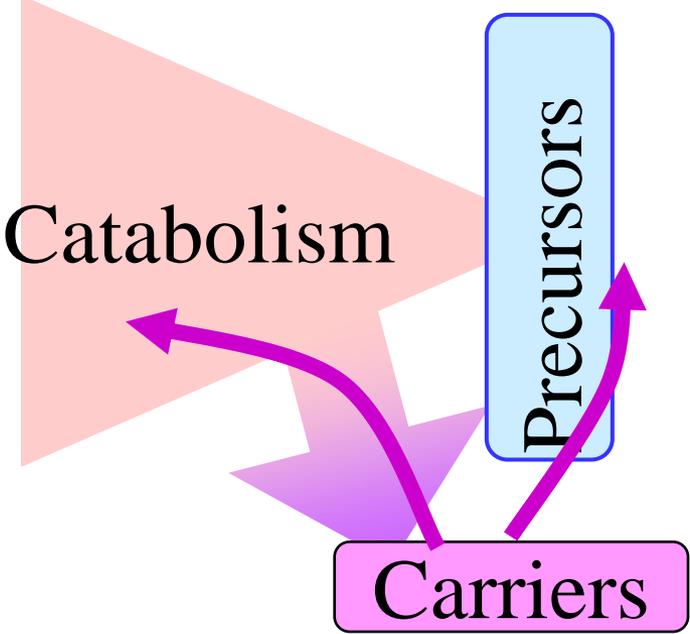
Core metabolic bowtie

Core
metabolism

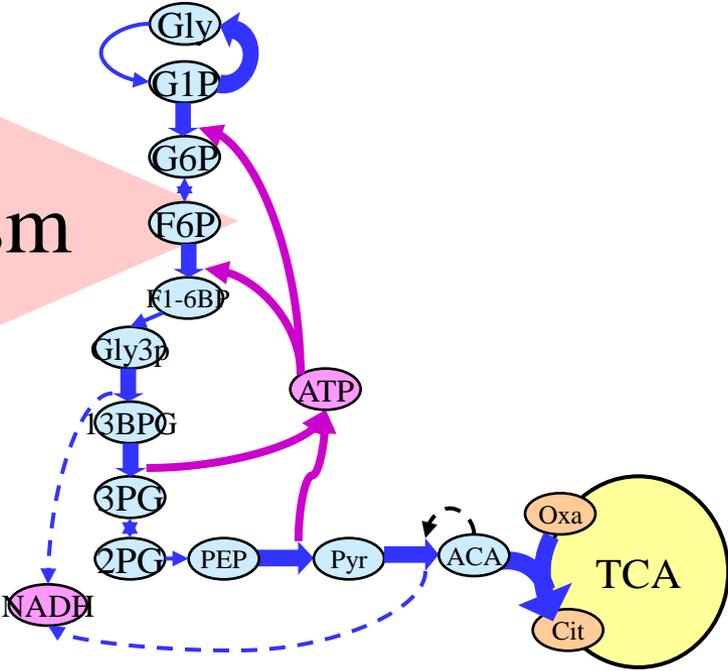
Catabolism

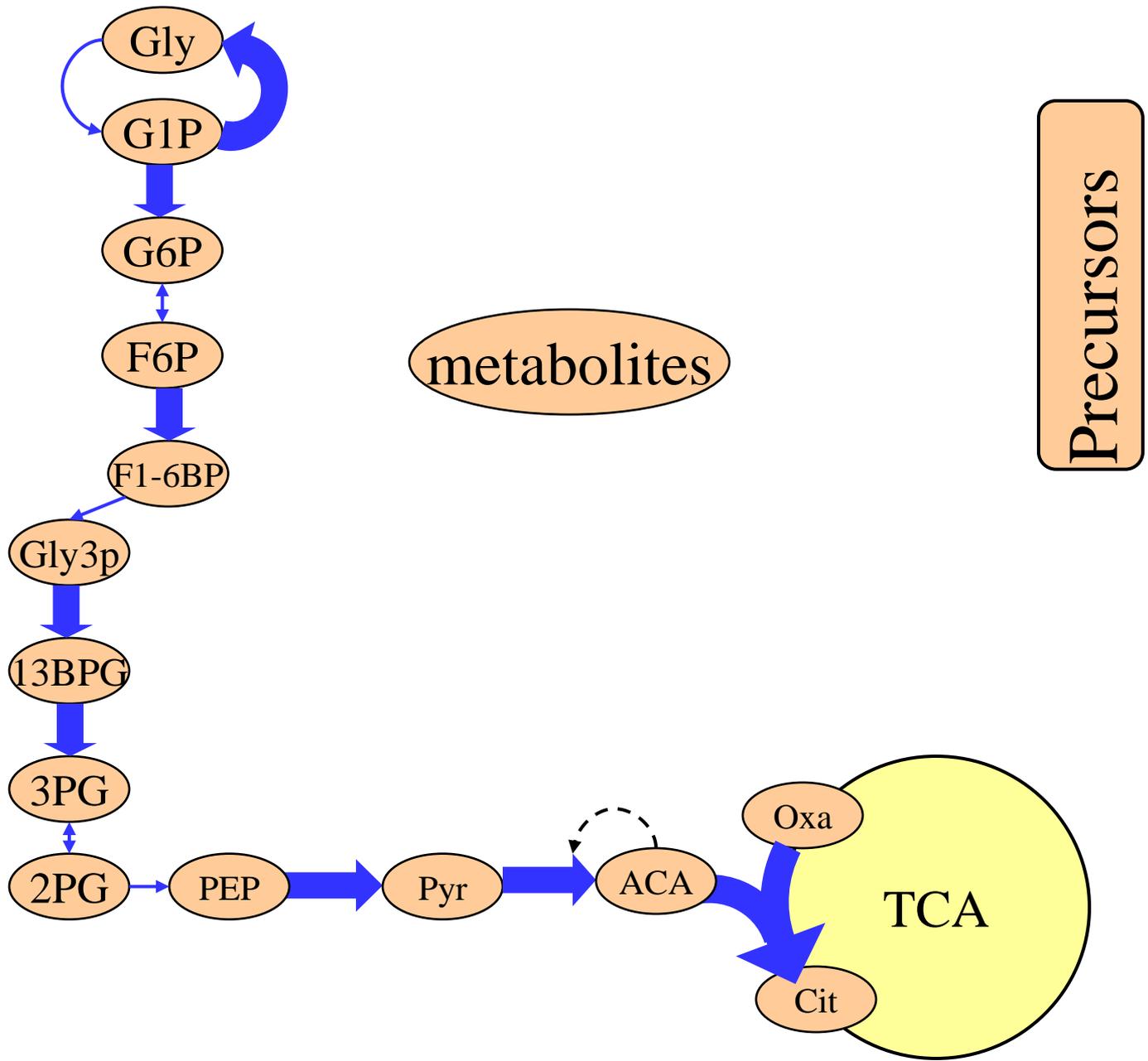
Inside every
cell ($\approx 10^{30}$)

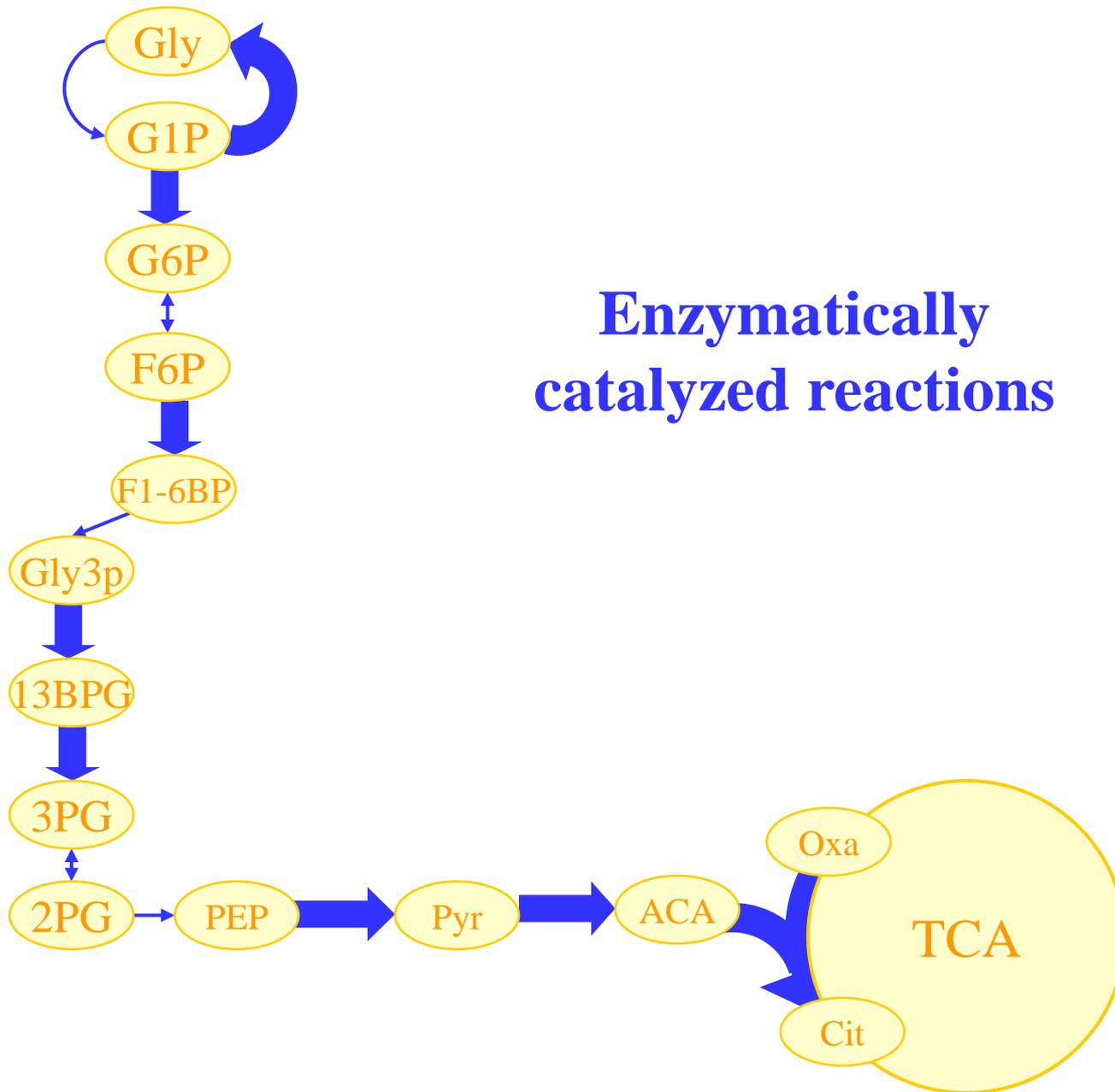


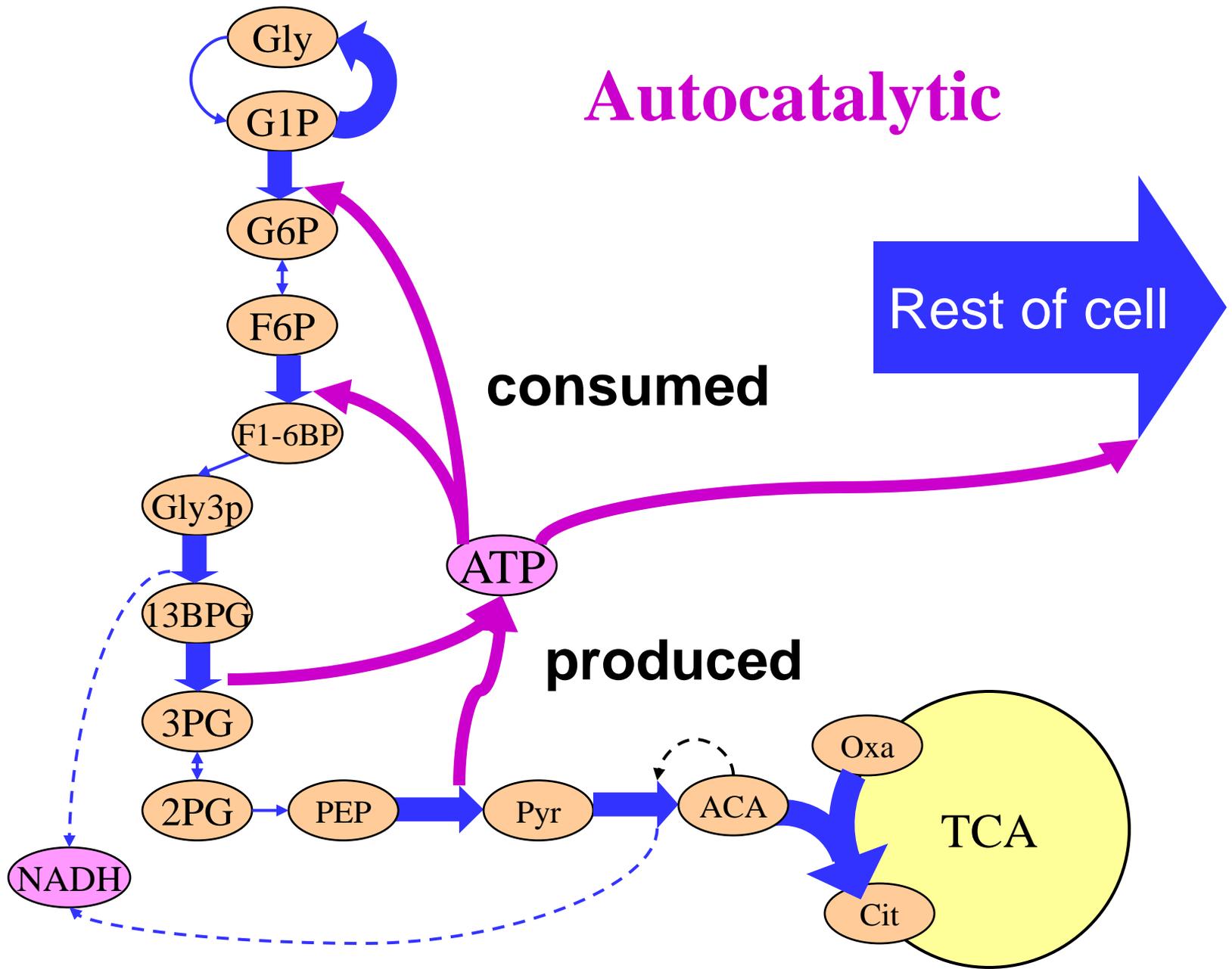


Catabolism

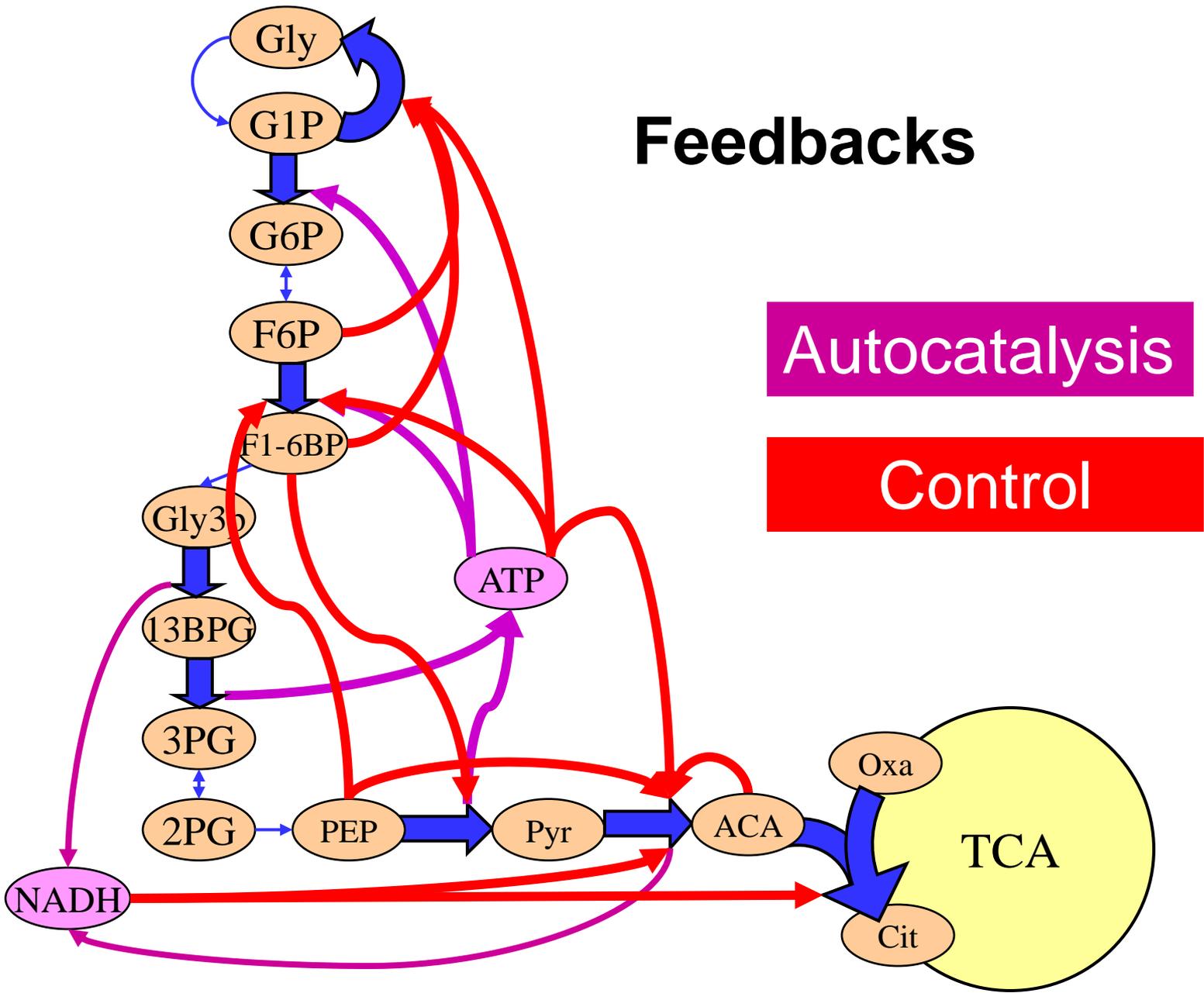


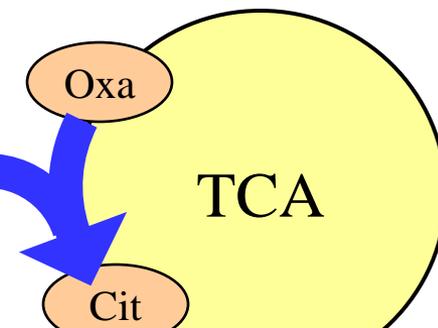
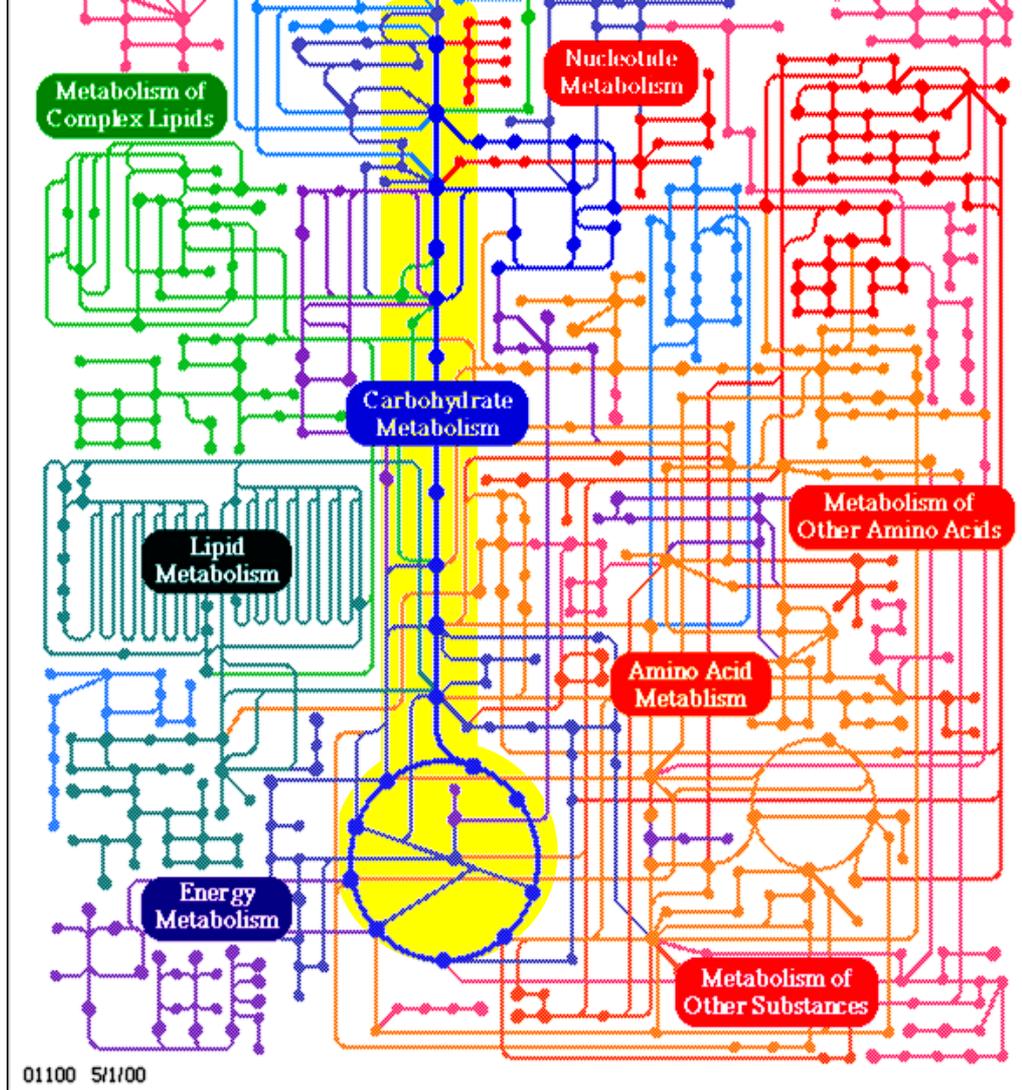
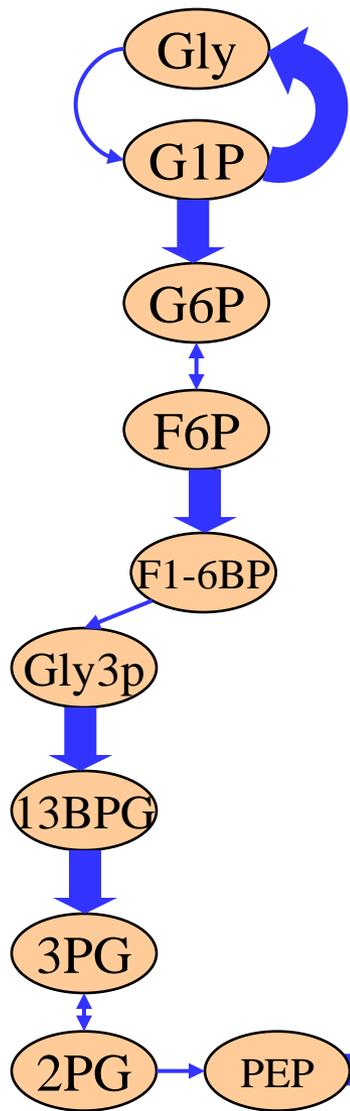


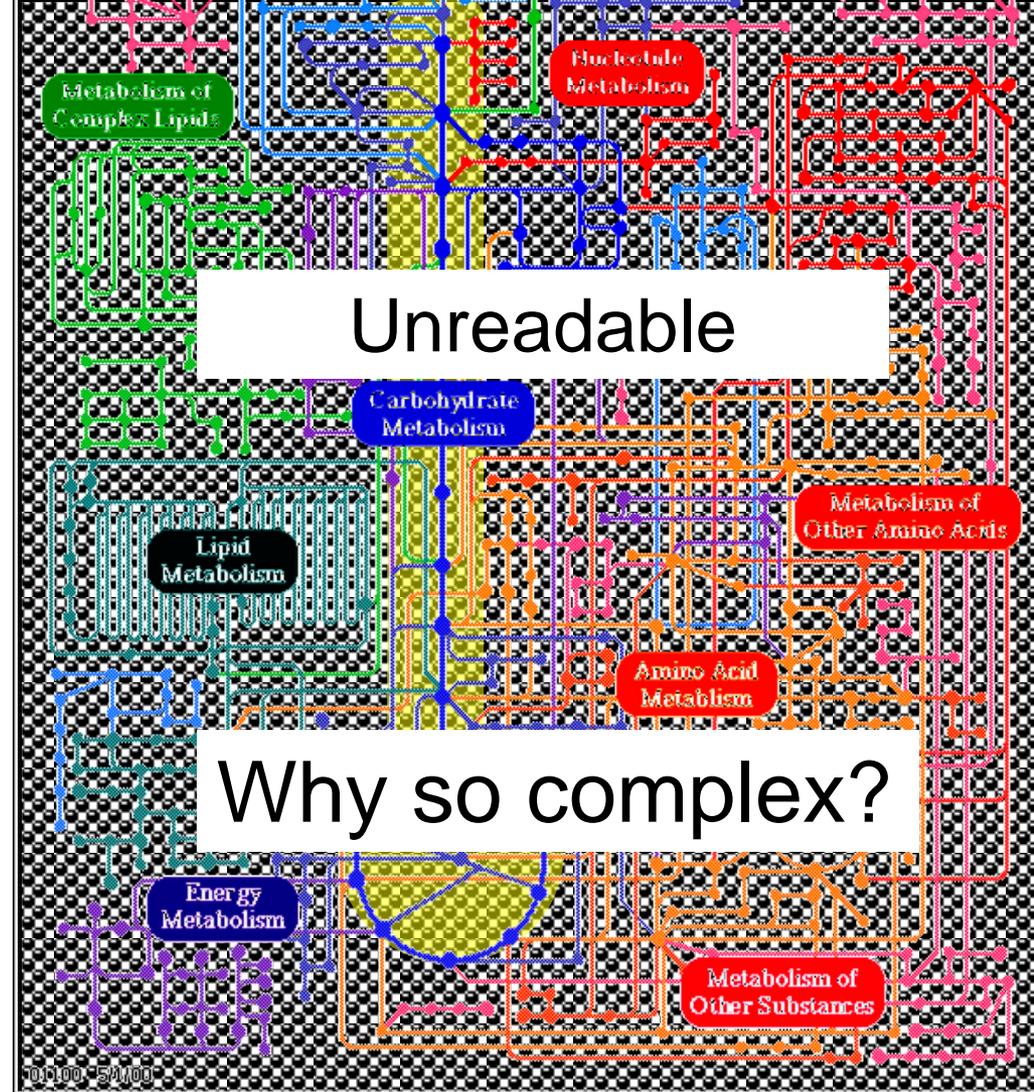
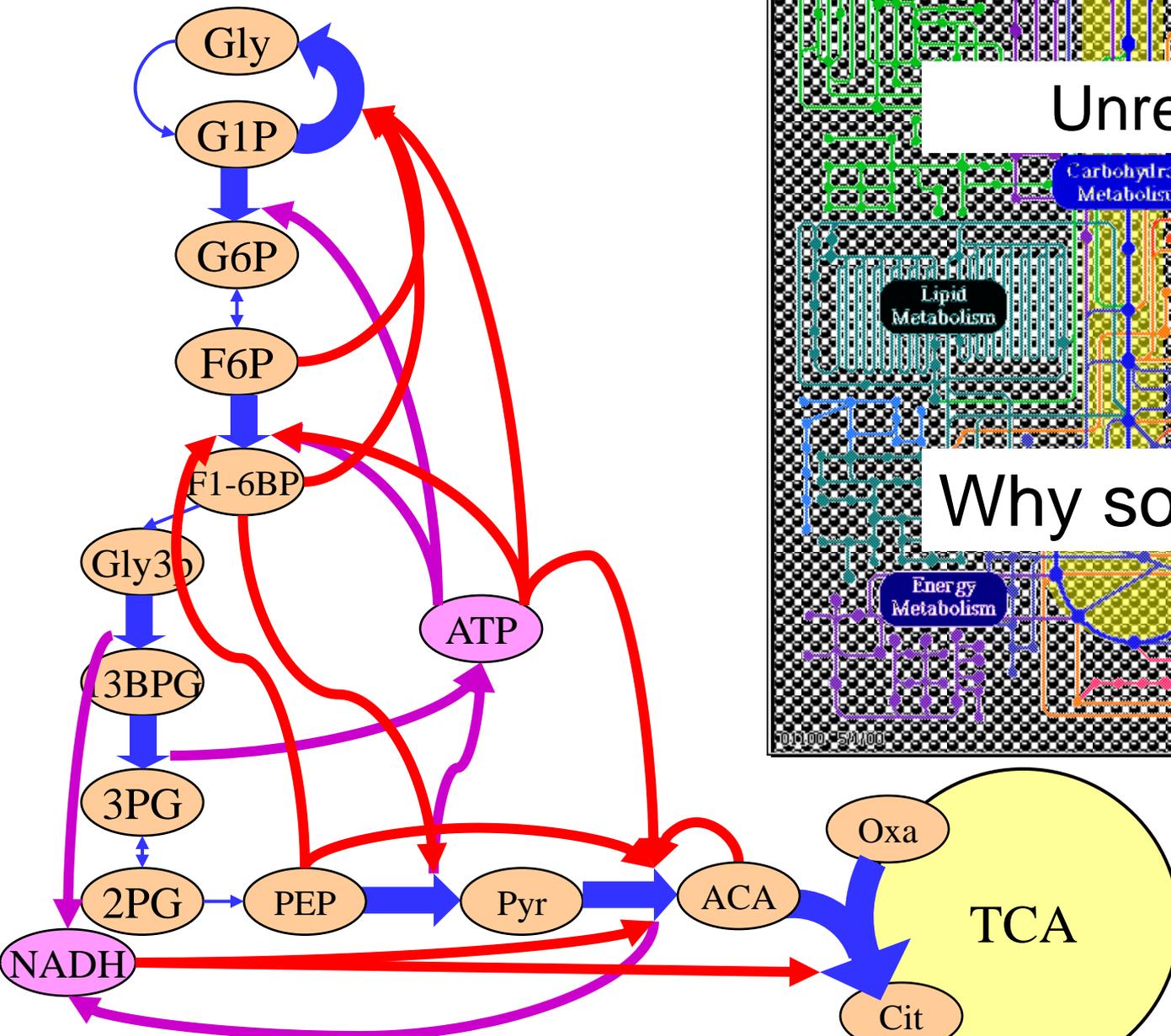




Feedbacks

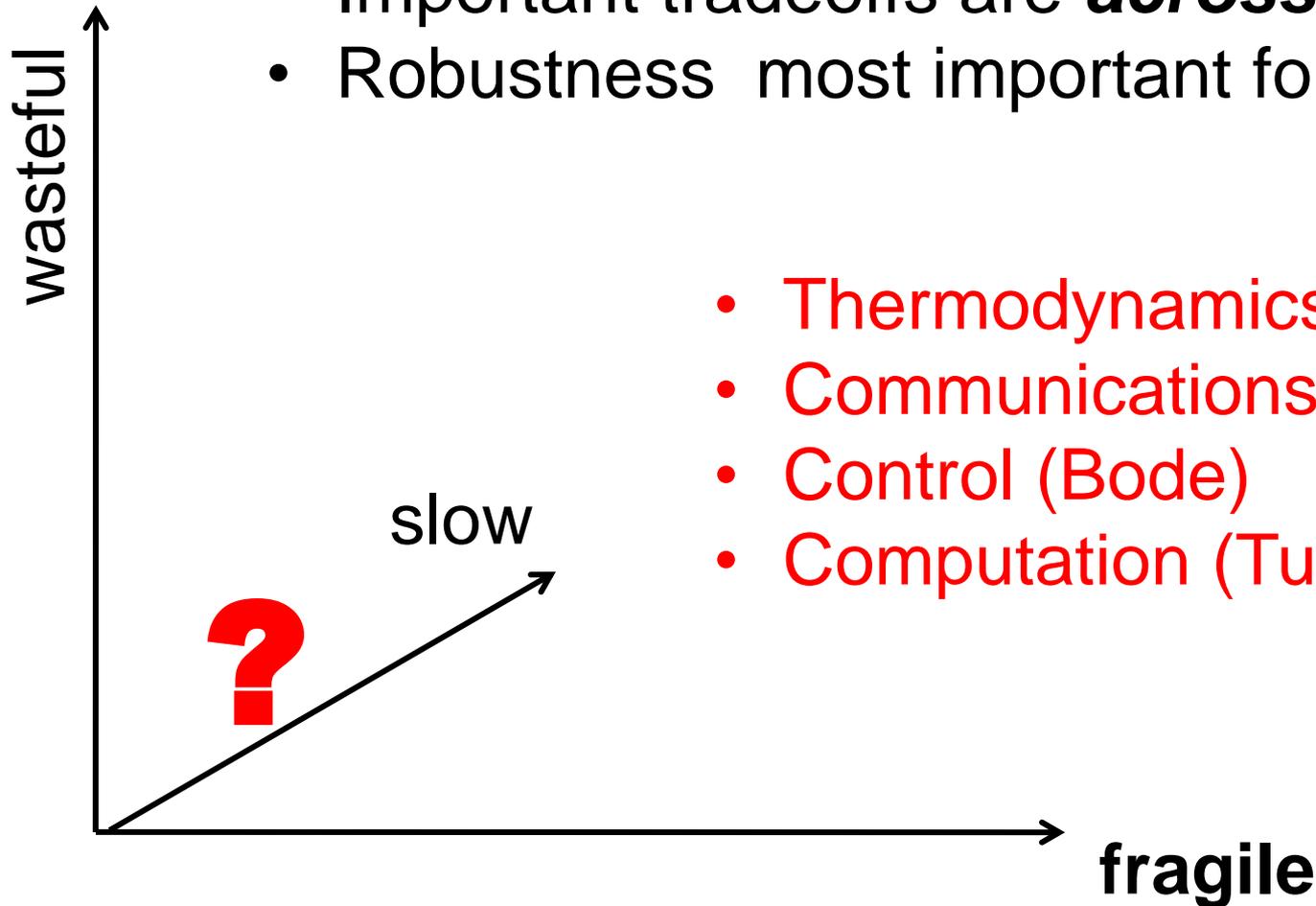






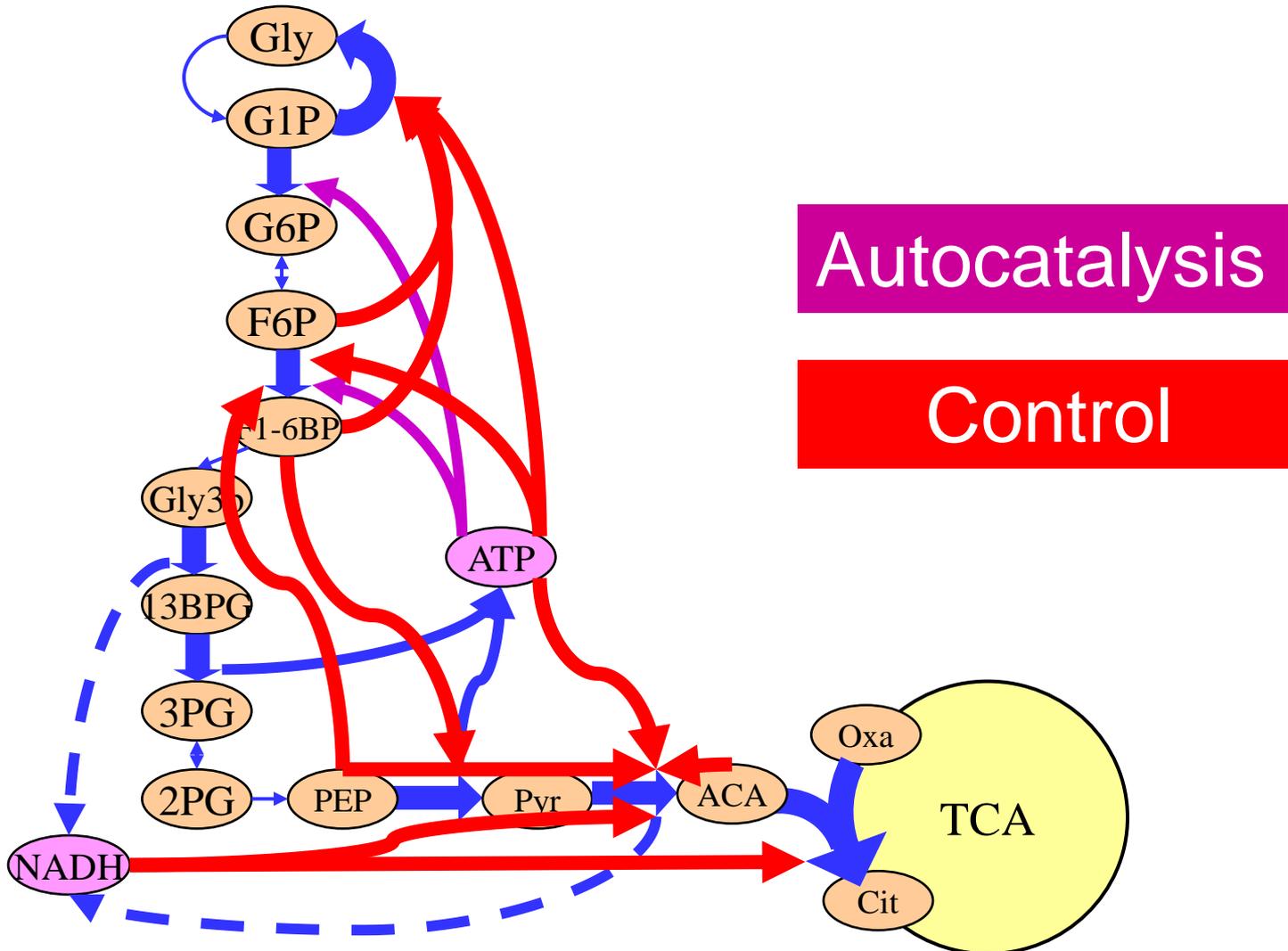
Hard tradeoffs

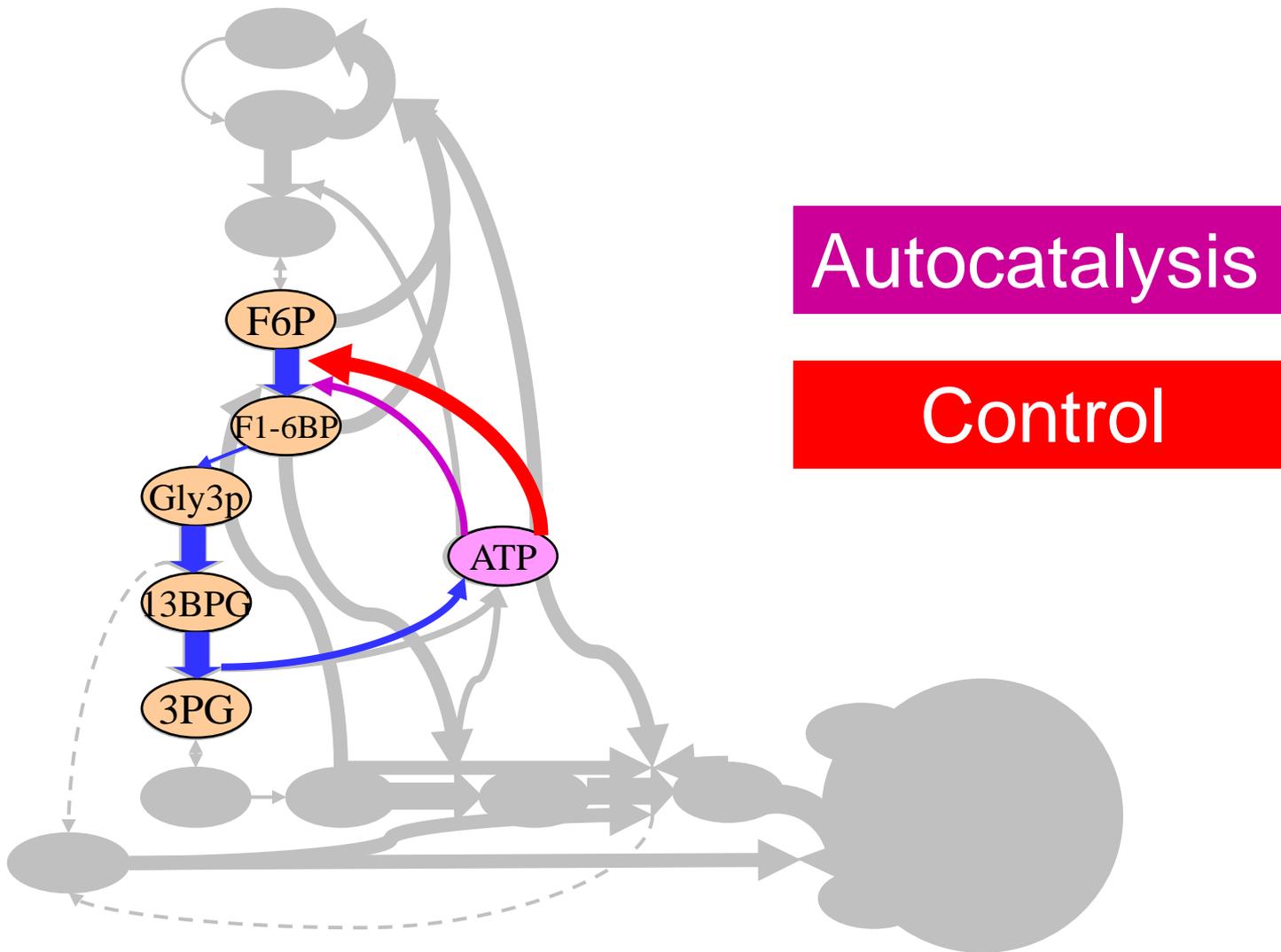
- Speed vs efficiency vs robustness vs ...
- Existing theories limited to one dimension
- Important tradeoffs are **across** these
- Robustness most important for complexity



- Thermodynamics (Carnot)
- Communications (Shannon)
- Control (Bode)
- Computation (Turing)

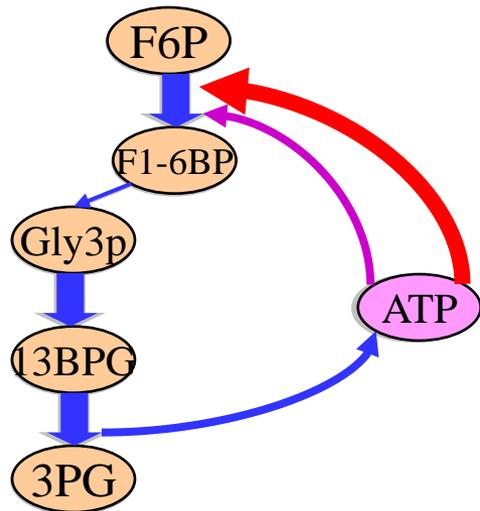
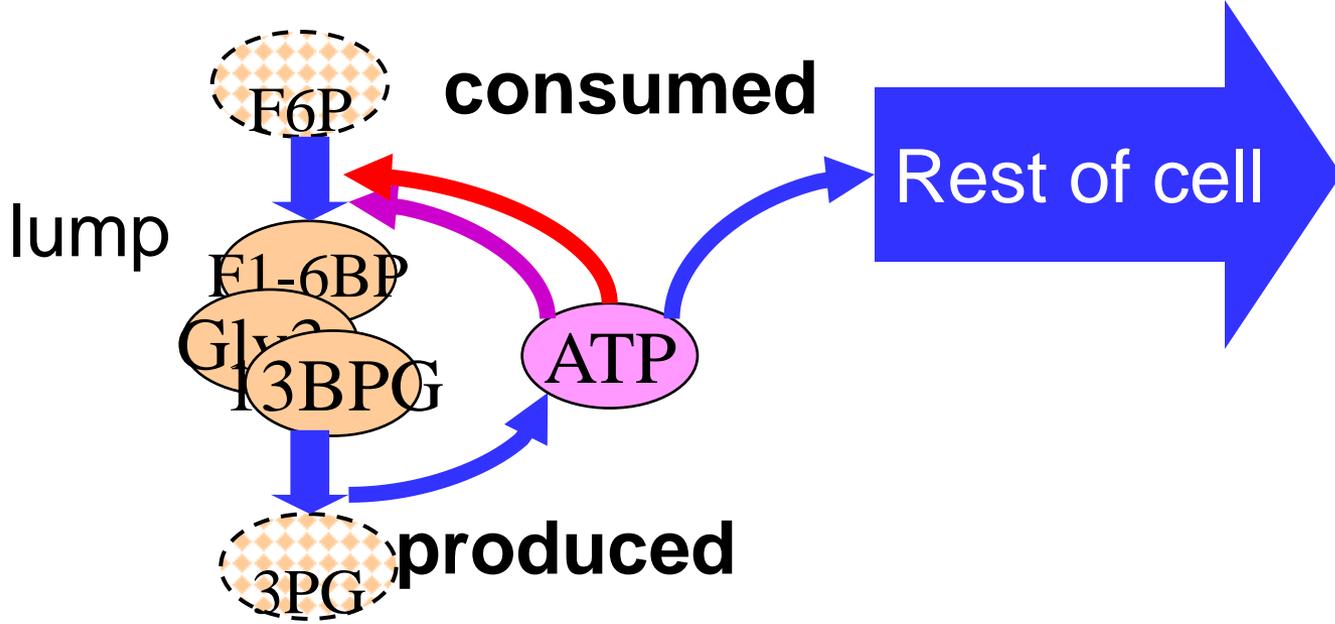
Feedbacks



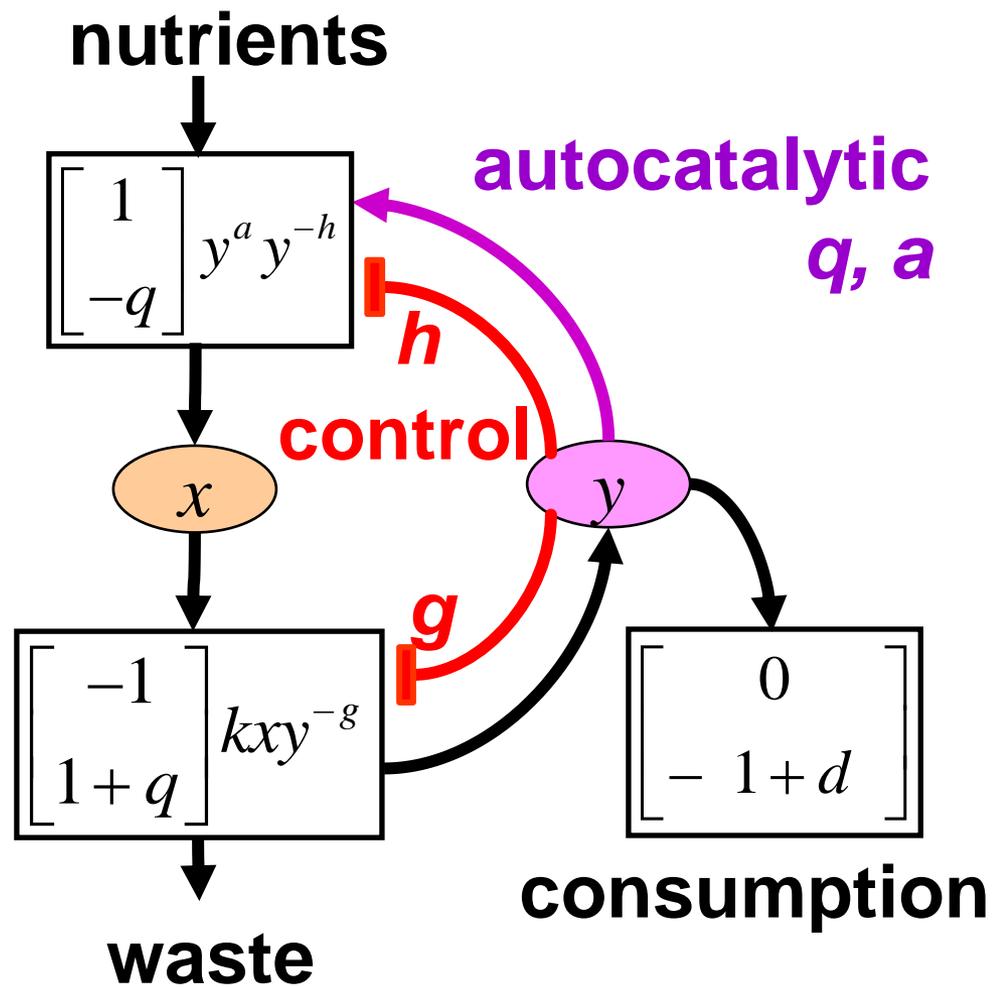
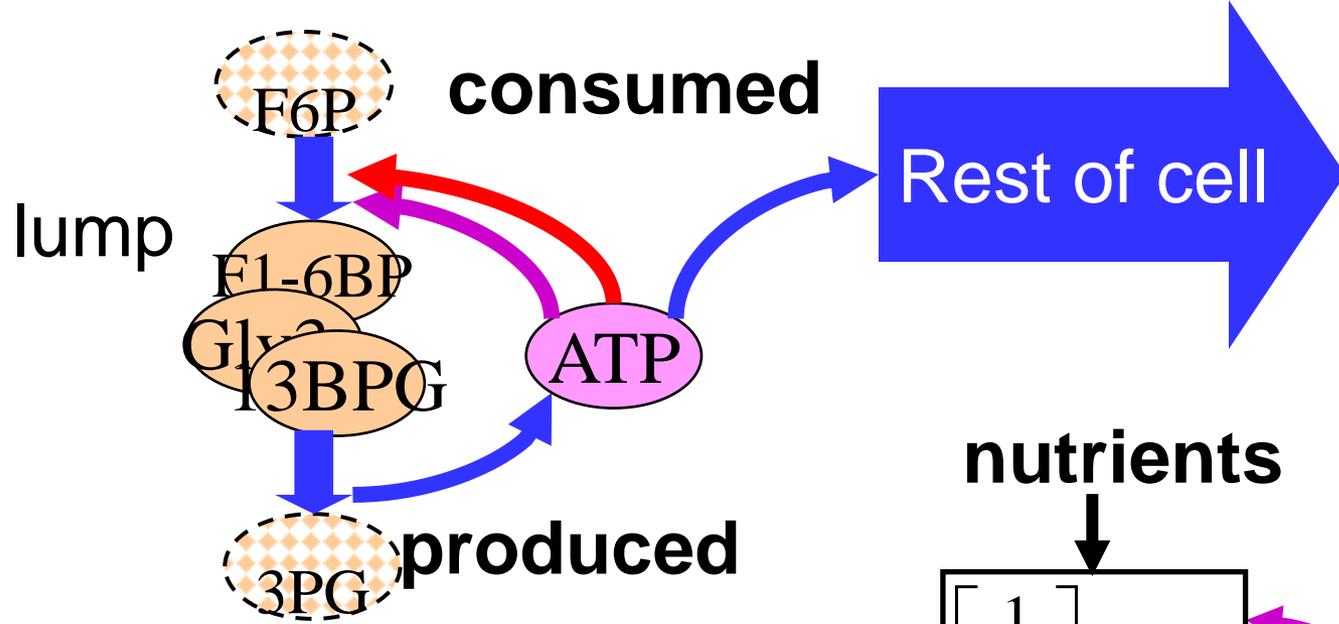


Autocatalysis

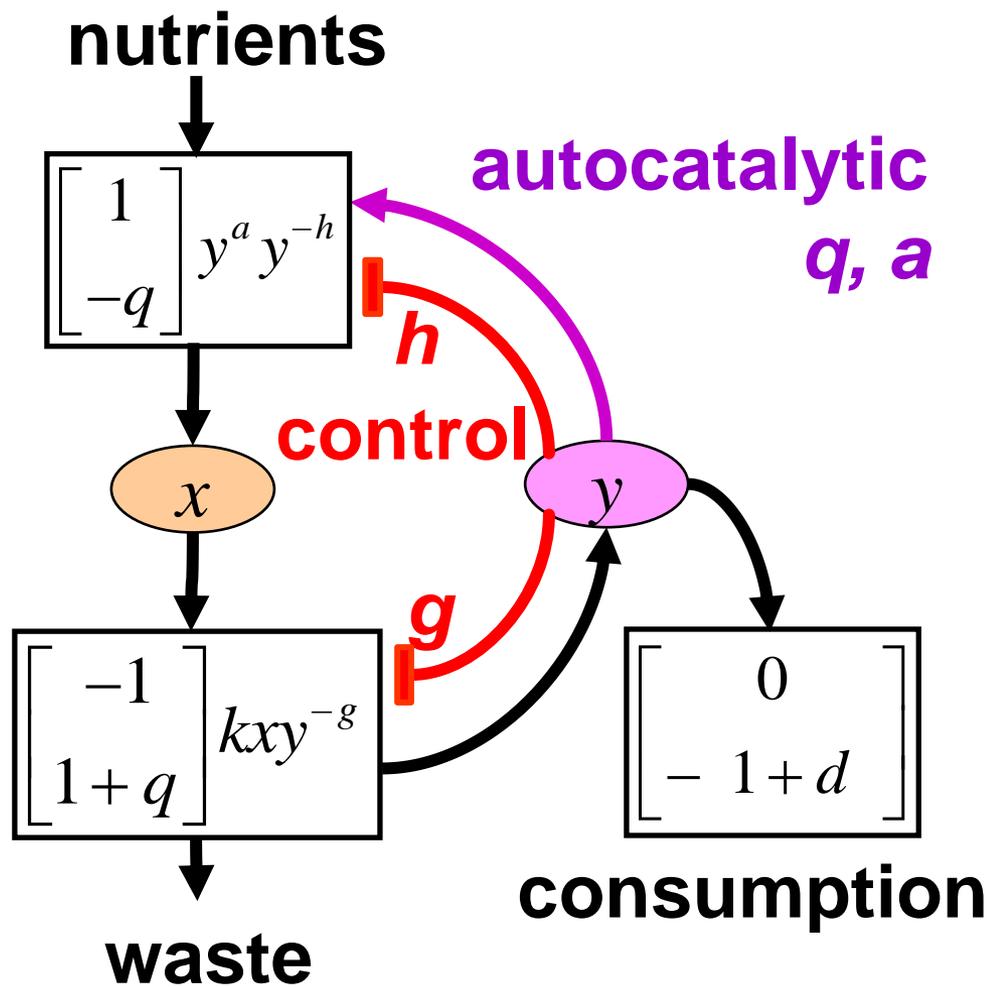
Control



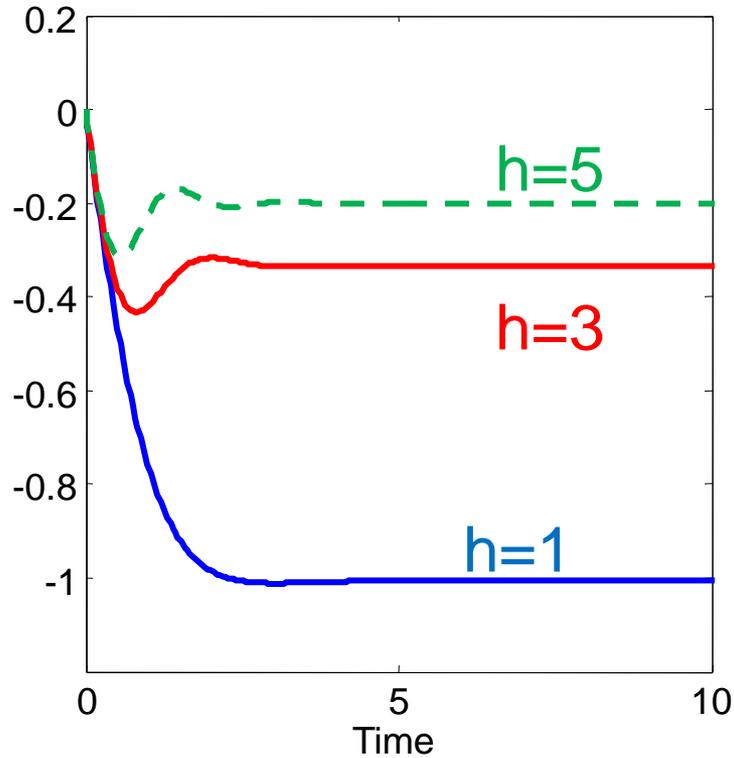
Control
Plus
Autocatalytic
Feedback



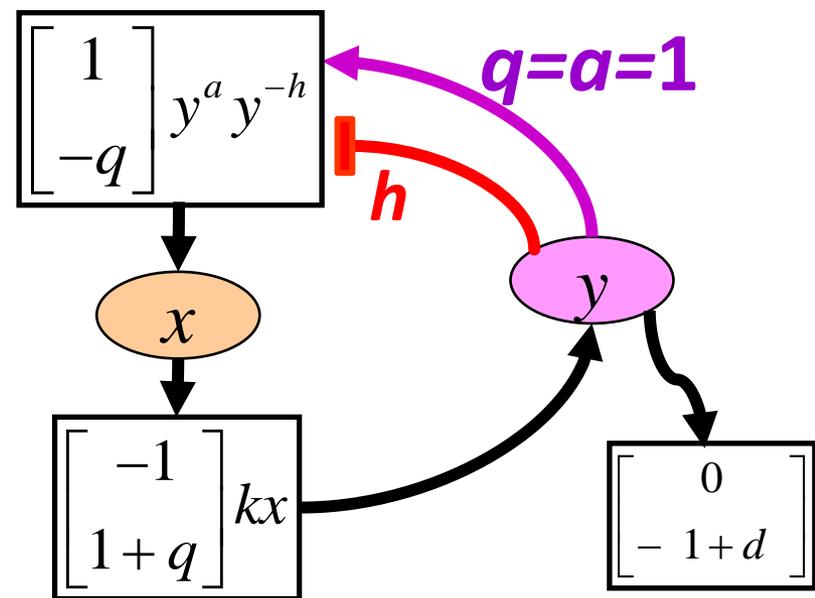
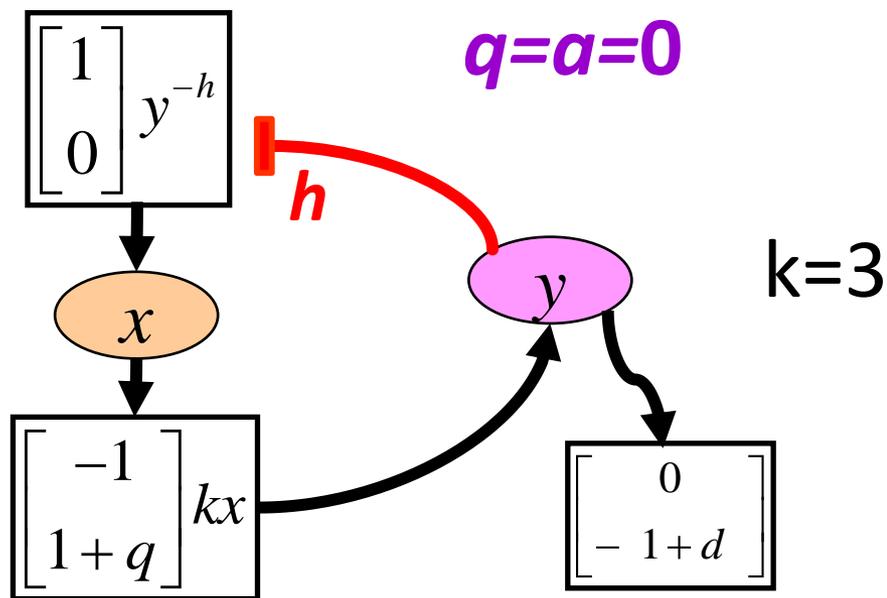
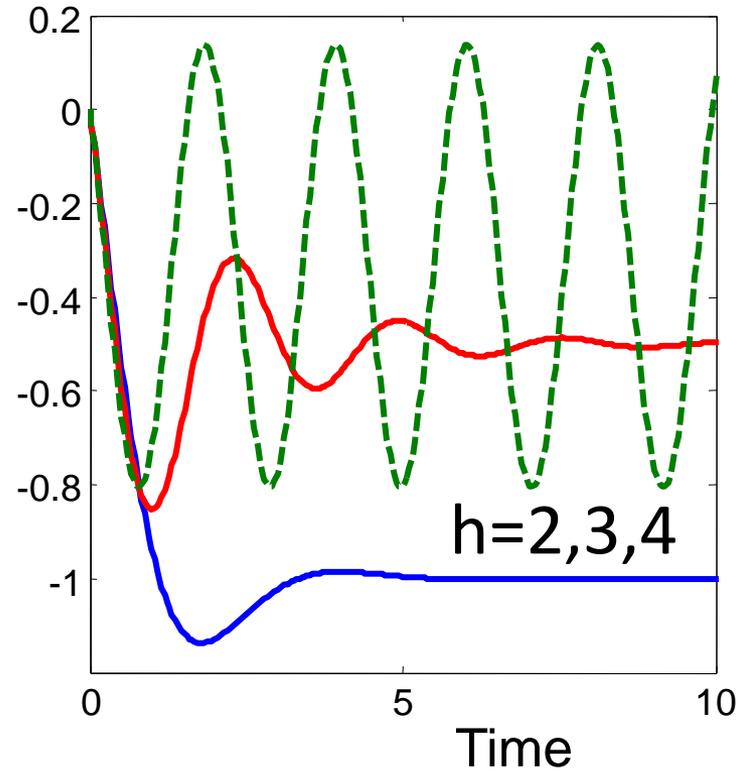
$$\frac{d}{dt} \begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} 1 \\ -q \end{bmatrix} y^a y^{-h} + \begin{bmatrix} -1 \\ 1+q \end{bmatrix} kxy^{-g} + \begin{bmatrix} 0 \\ -1+d \end{bmatrix}$$



Time Simulation



Time Simulation

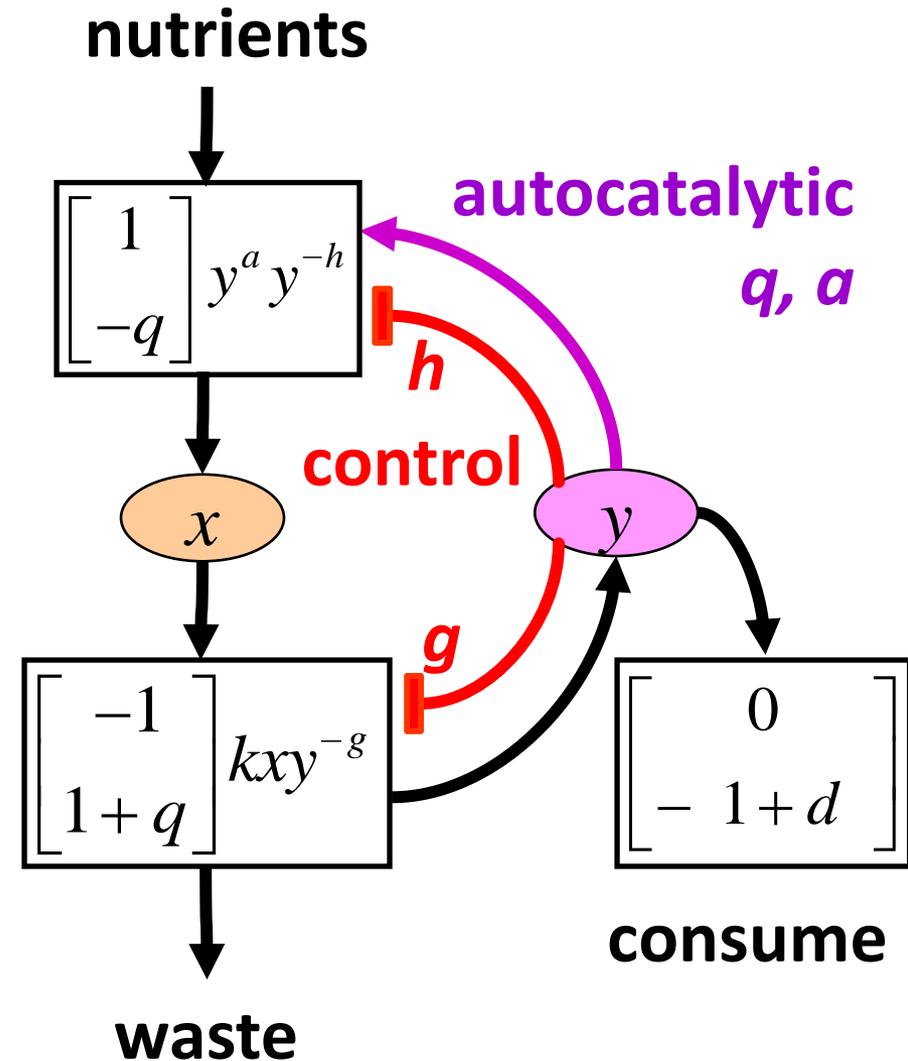


Quantify tradeoffs

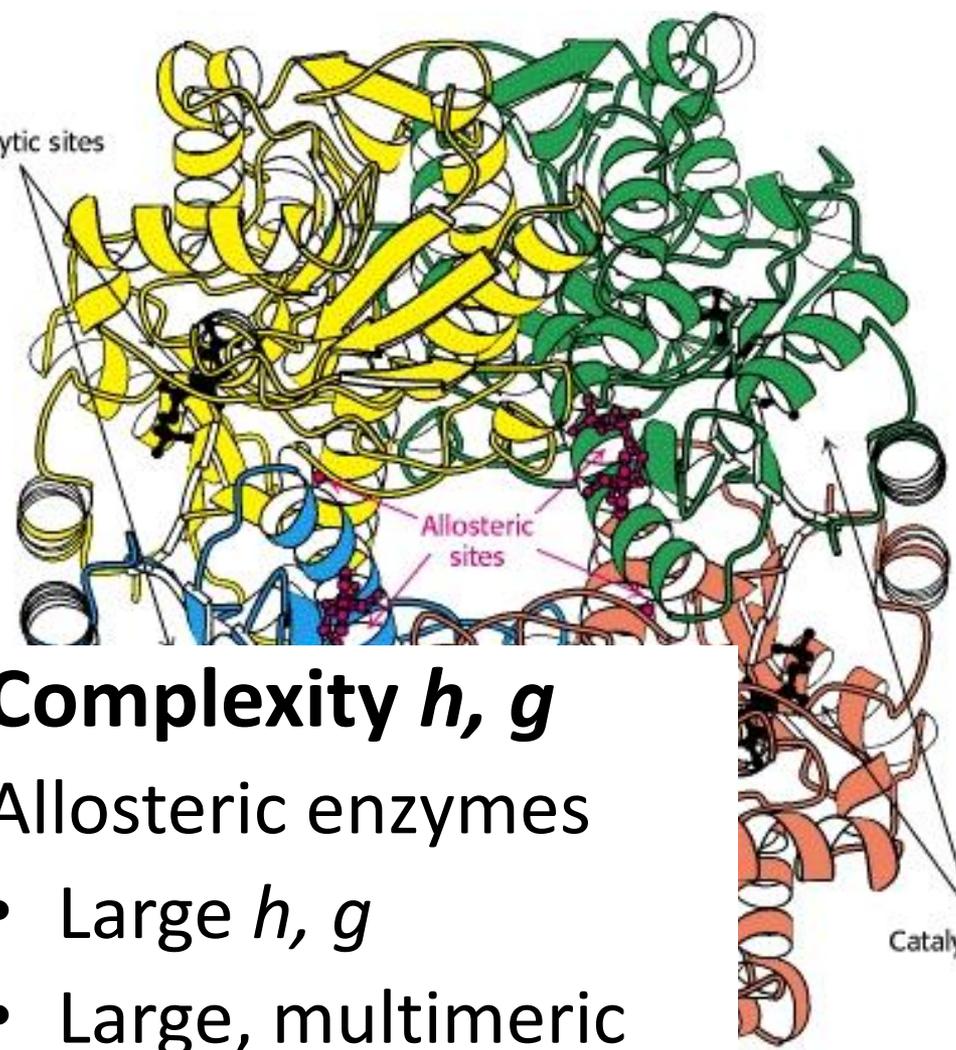
(x, y, d) = signals

(q, a, k, h, g) = “constants”

- Complexity
 - Enzymes
 - Network
- Metabolic Overhead
 - Enzyme complexity
 - Enzyme amount
 - Autocatalysis
 - Waste/Nutrients
- Fragility
 - Disturbance rejection
 - Stability



Catalytic sites



Complexity h, g

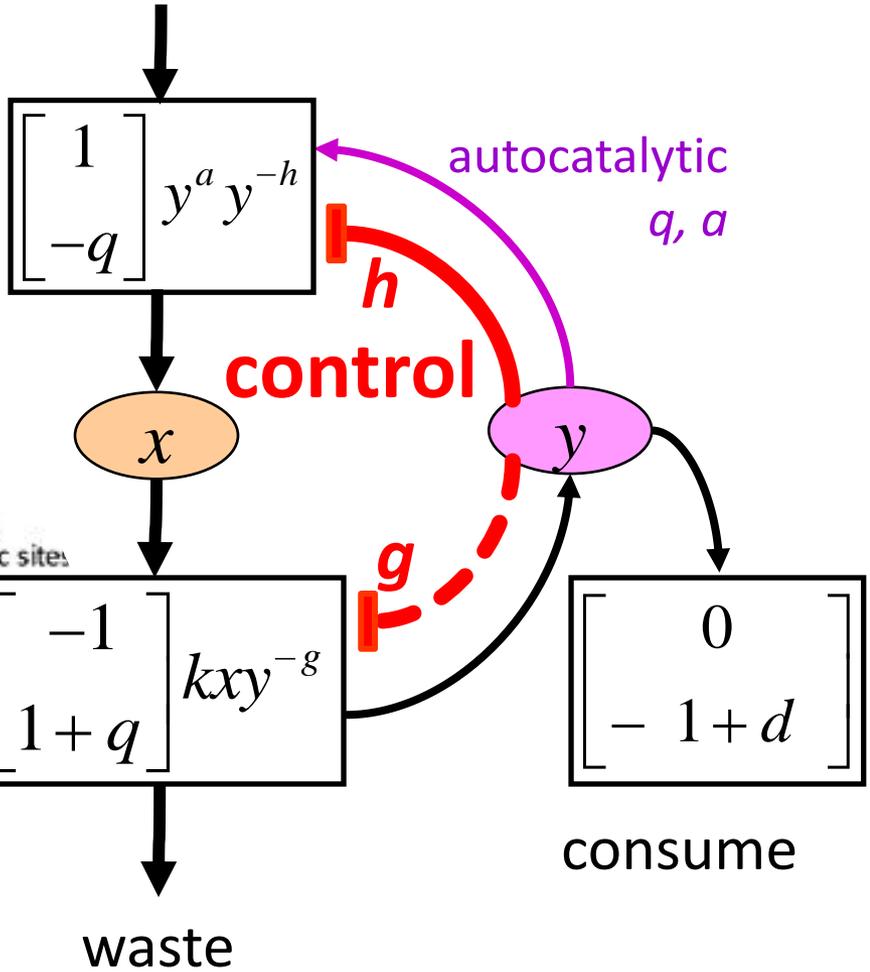
Allosteric enzymes

- Large h, g
- Large, multimeric
- Nonlinearity

Control “topology”

- $g > 0$?

nutrients



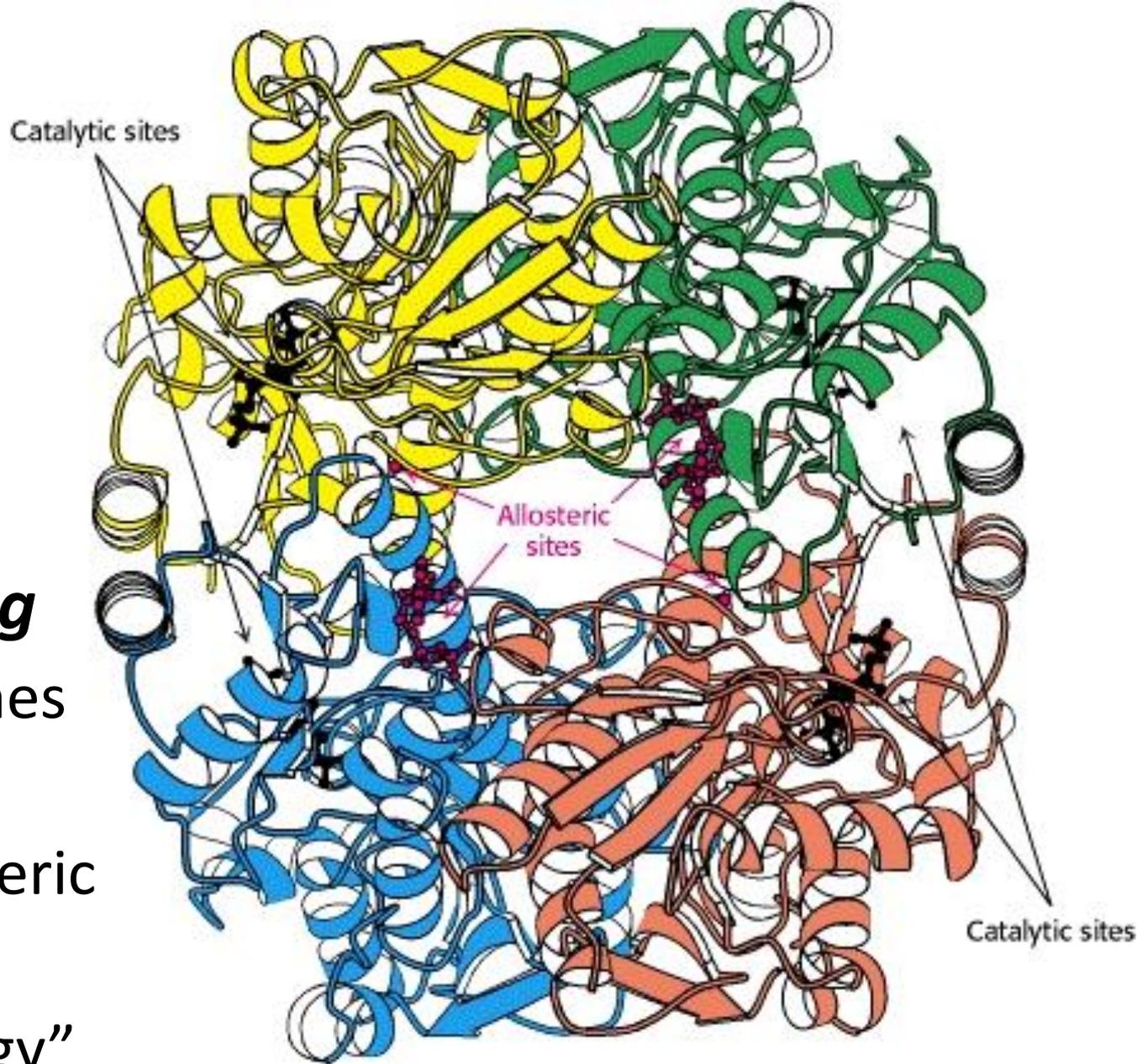
Complexity h, g

Allosteric enzymes

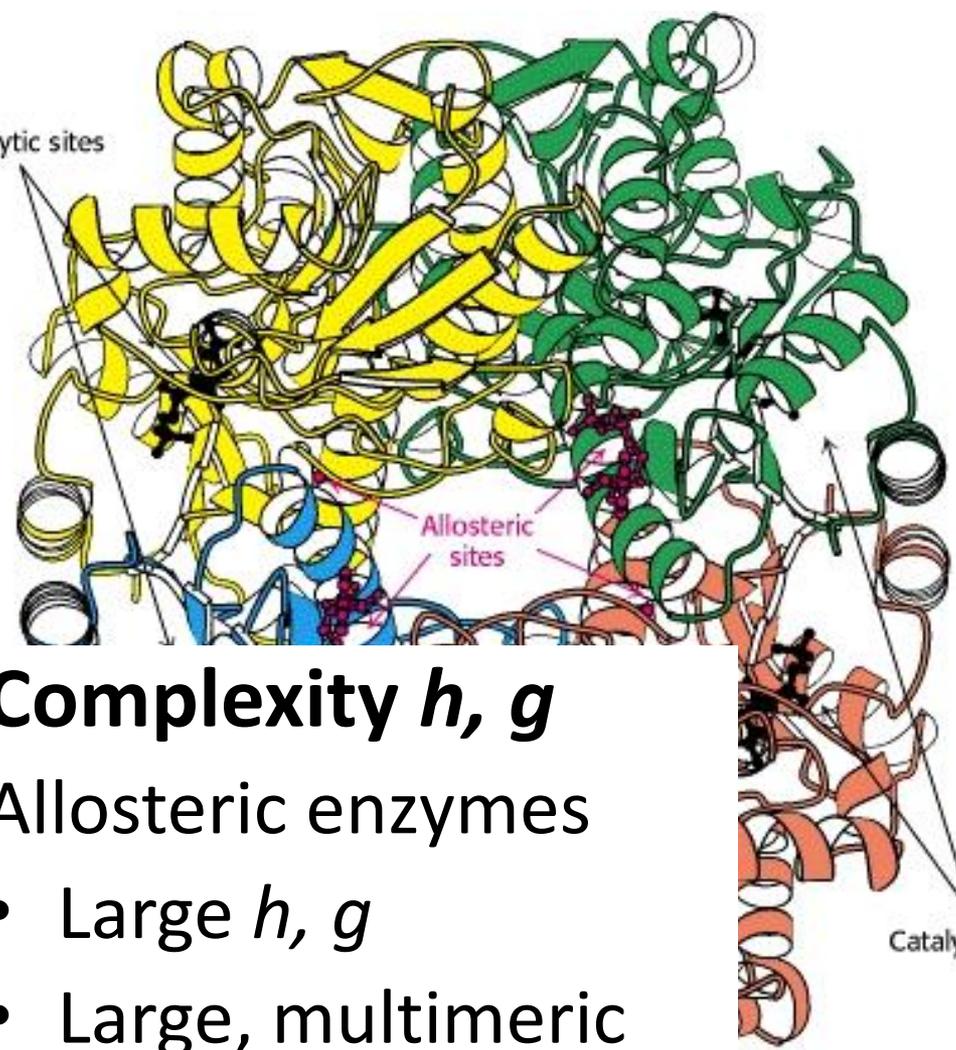
- Large h, g
- Large, multimeric
- Nonlinearity

Control “topology”

- $g > 0$?



Catalytic sites



Complexity h, g

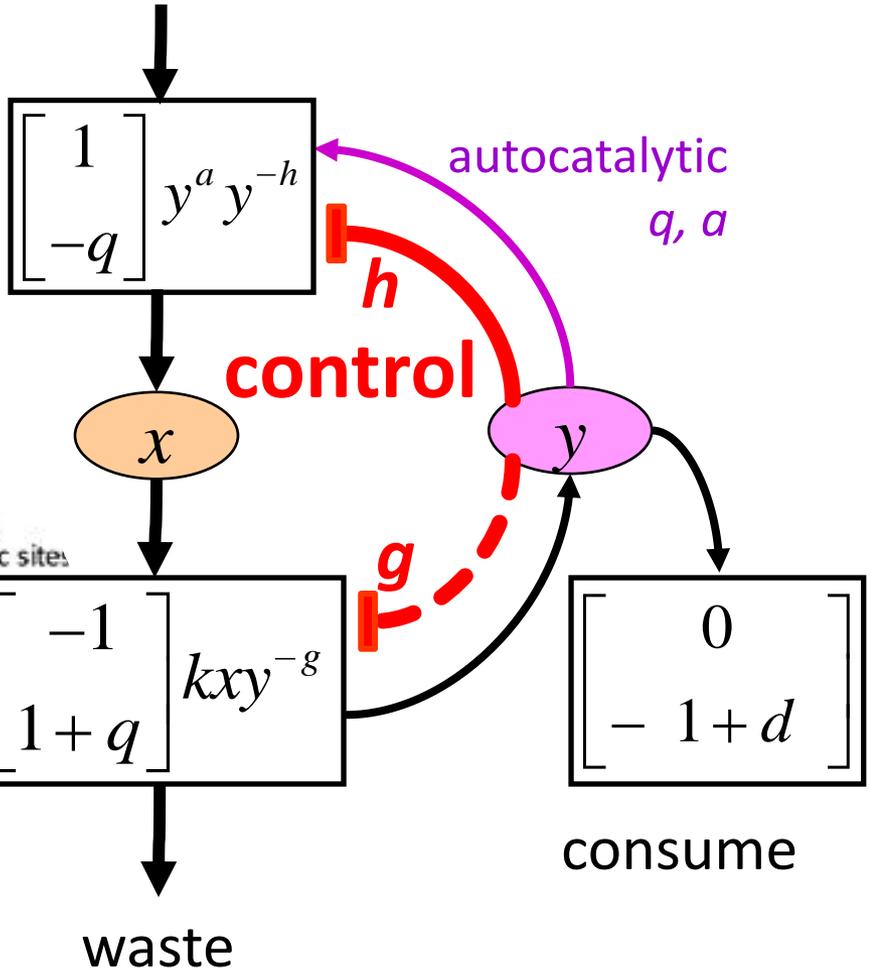
Allosteric enzymes

- Large h, g
- Large, multimeric
- Nonlinearity

Control “topology”

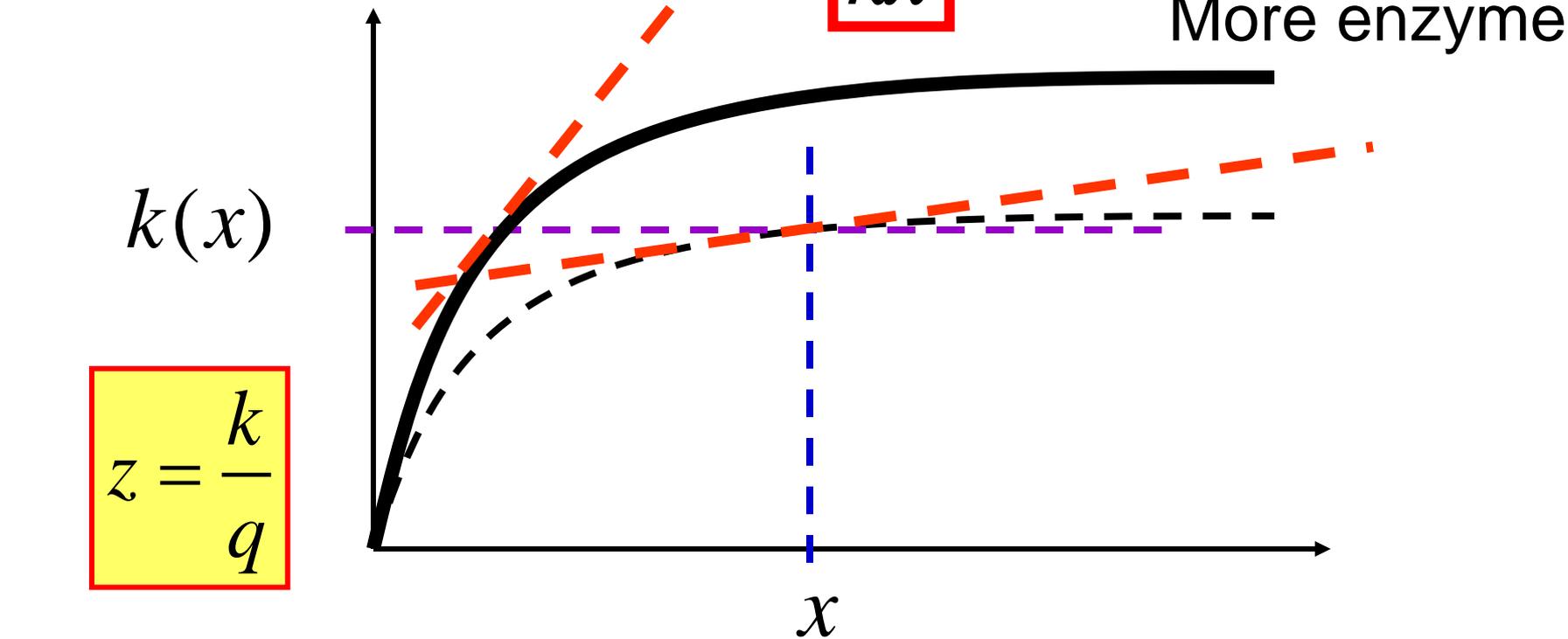
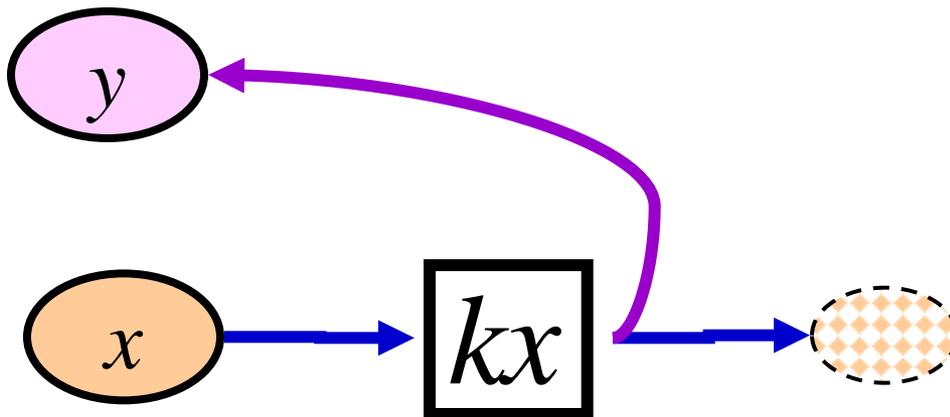
- $g > 0$?

nutrients

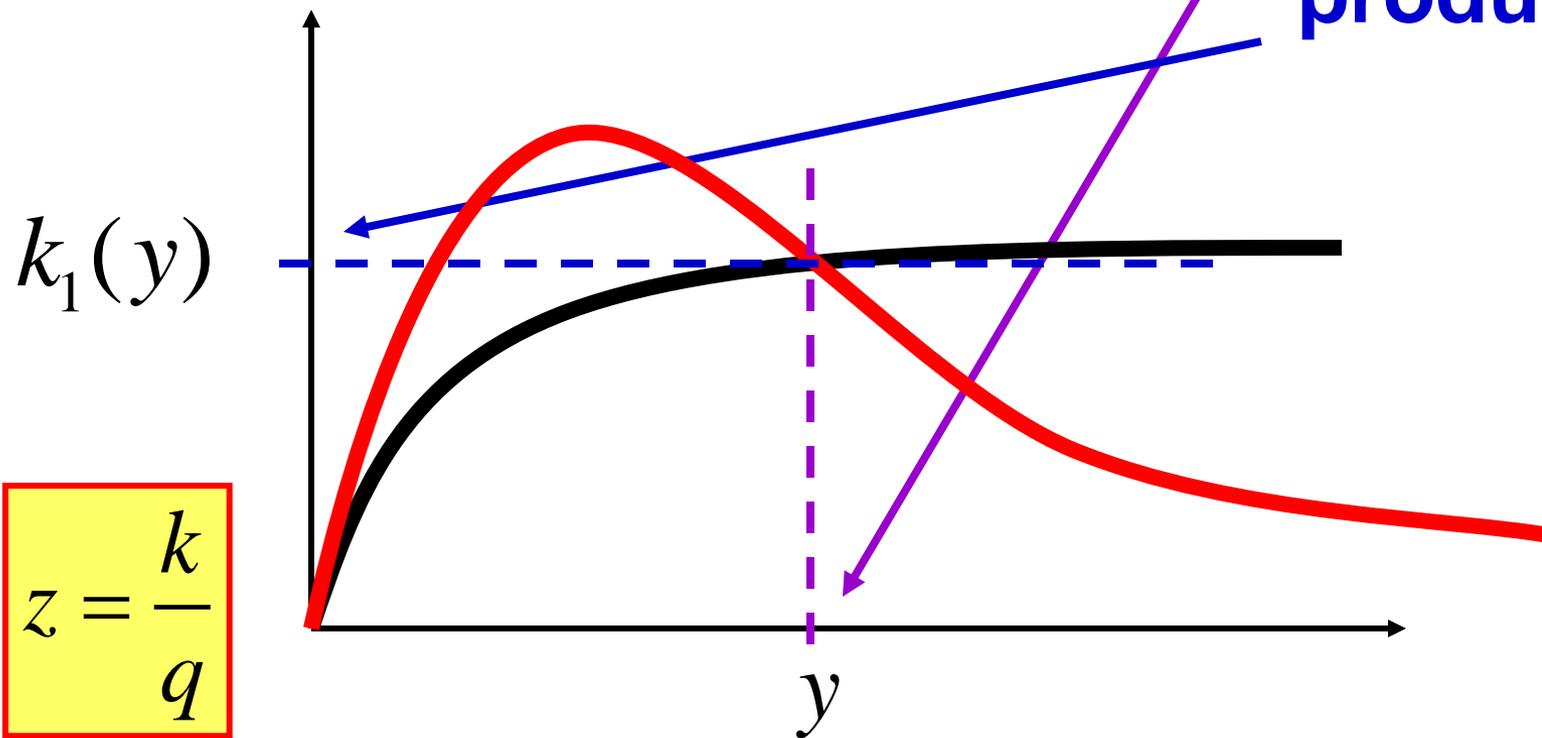
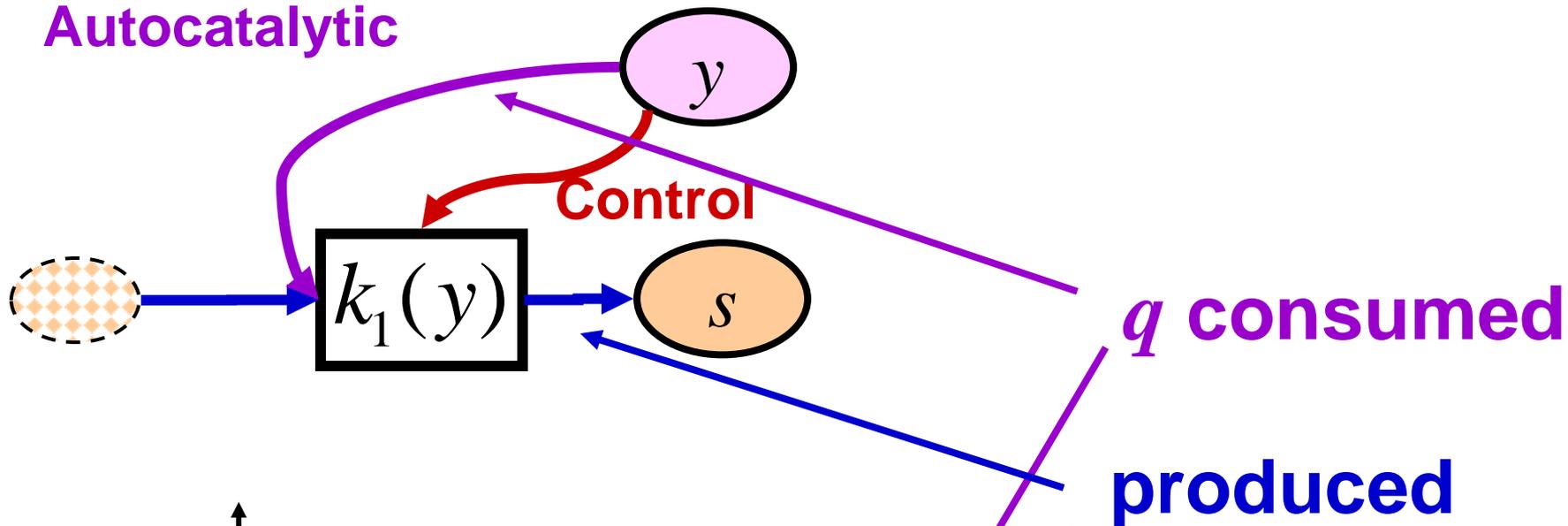


rate

level



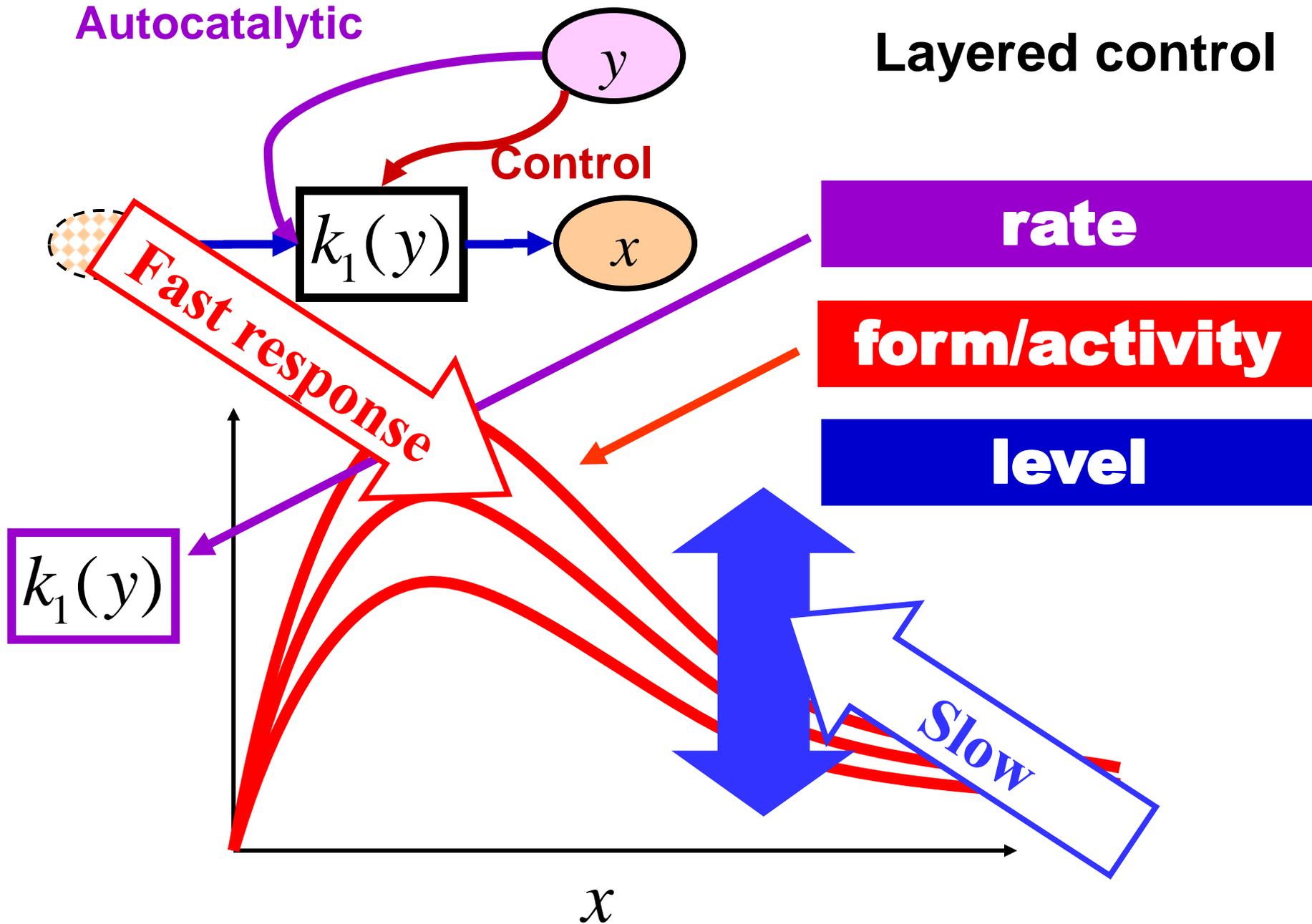
Autocatalytic



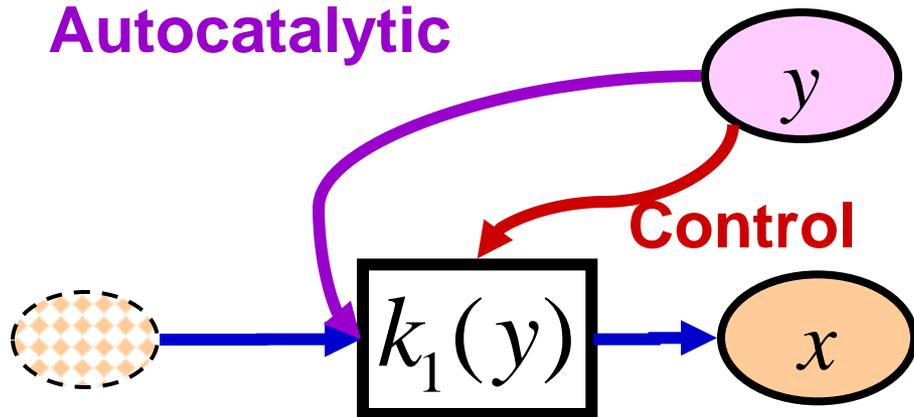
$$z = \frac{k}{q}$$

Autocatalytic

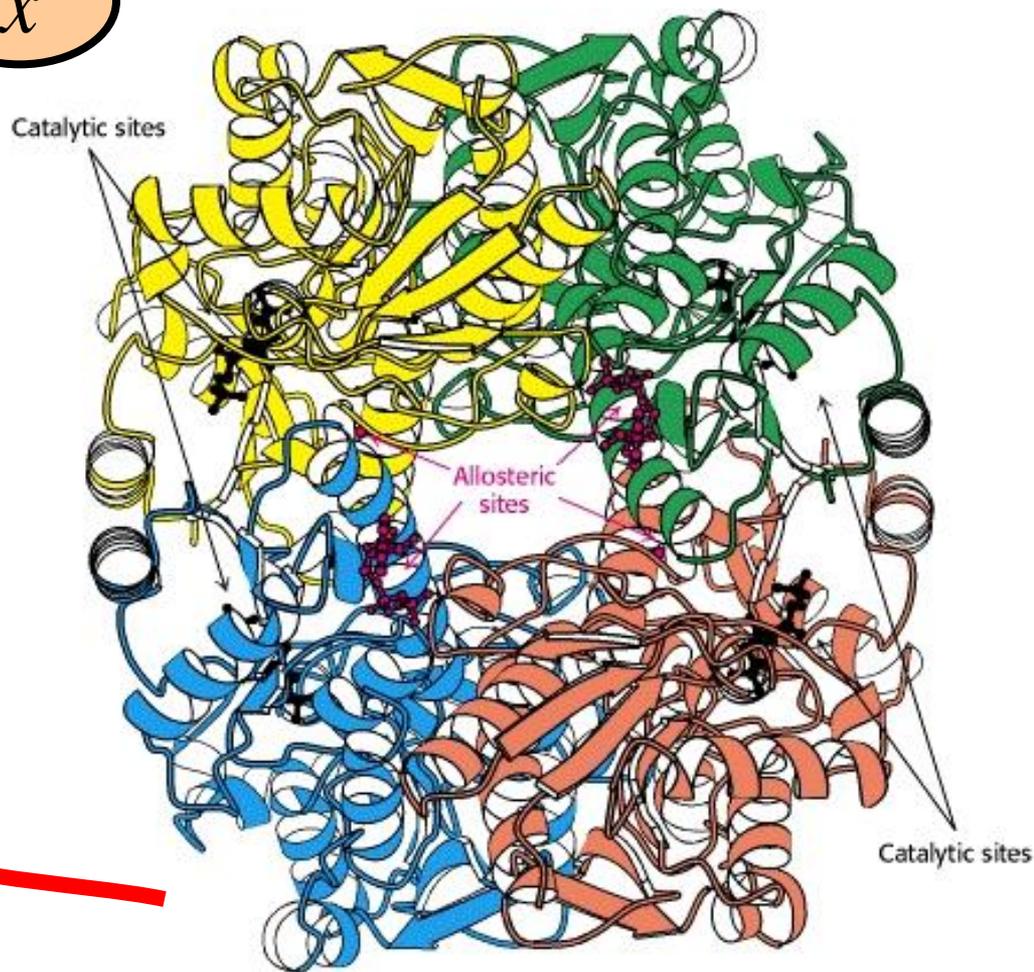
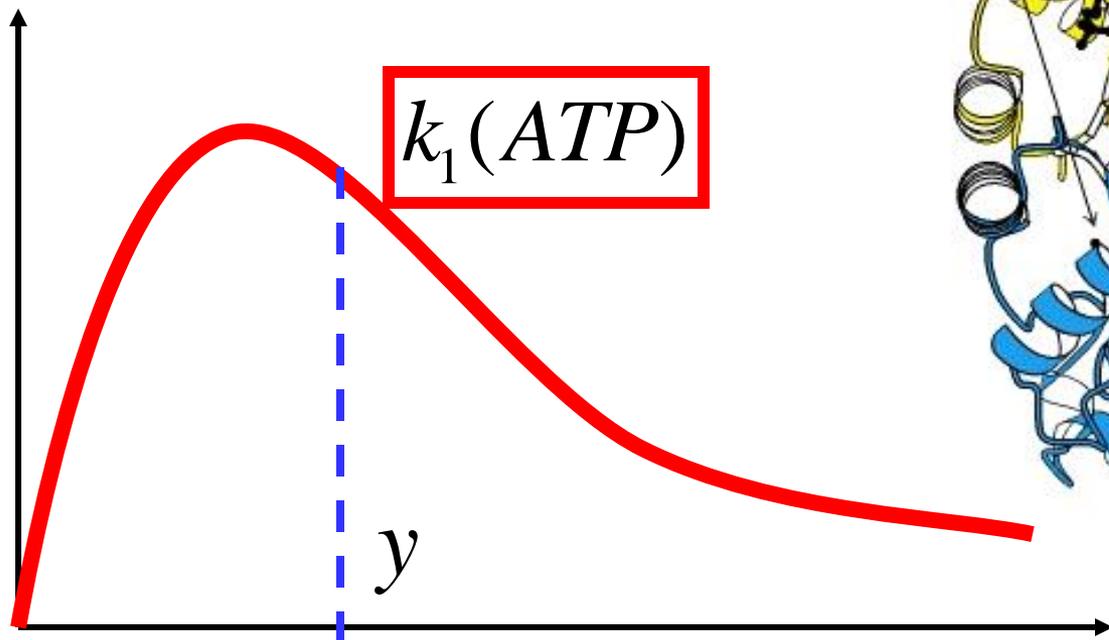
Layered control

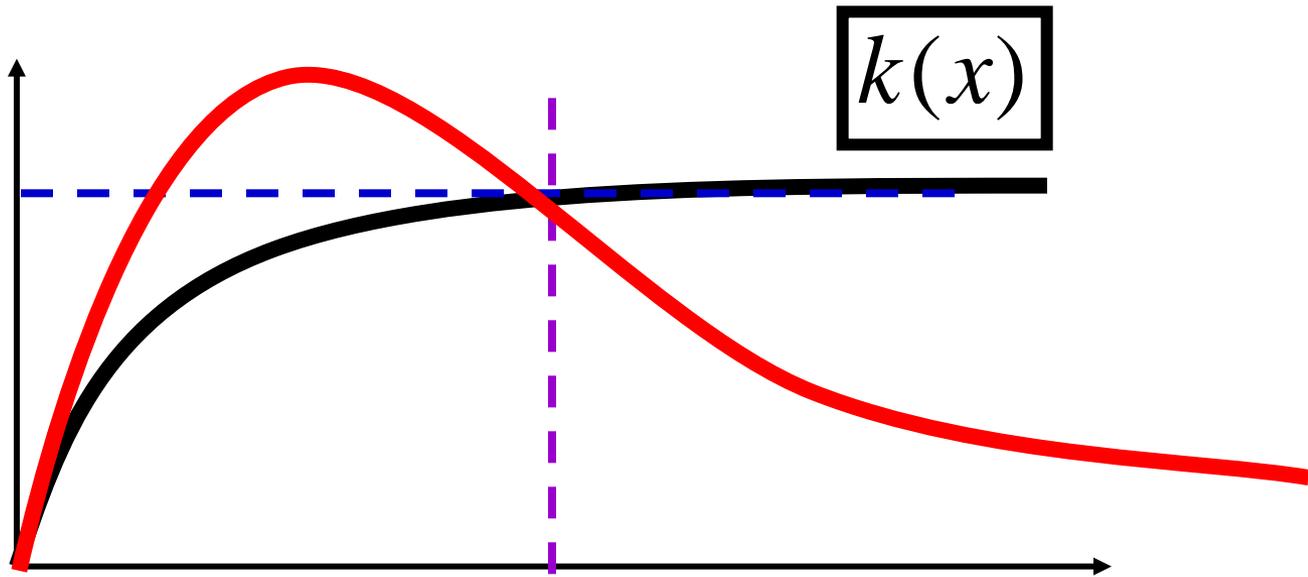
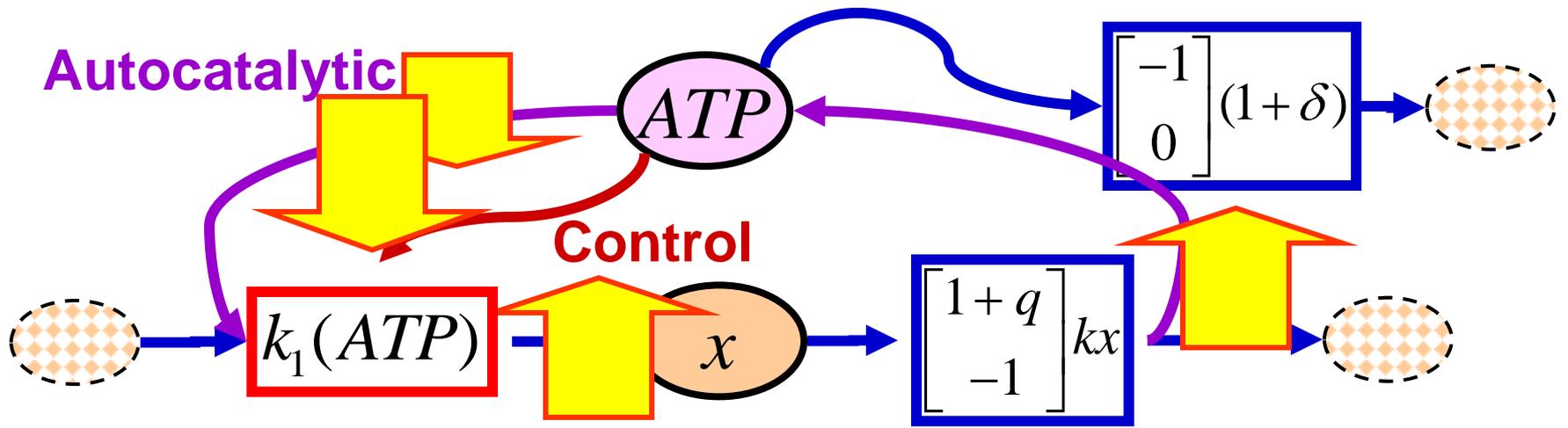


Autocatalytic



Enzyme
complexity





high \ large	<i>h</i>	<i>g</i>	<i>k</i>	<i>q</i>	<i>a</i>
↑Complexity	↑	↑		↑	↑

high \ large	<i>h</i>	<i>g</i>	<i>k</i>	<i>q</i>	<i>a</i>
↑Complexity	+	+		+	+

Metabolic overhead

h, g, k, q

- Large enzymes (h, g)
- Enzyme amount $\approx k$
- Autocatalysis q, a

Assume:

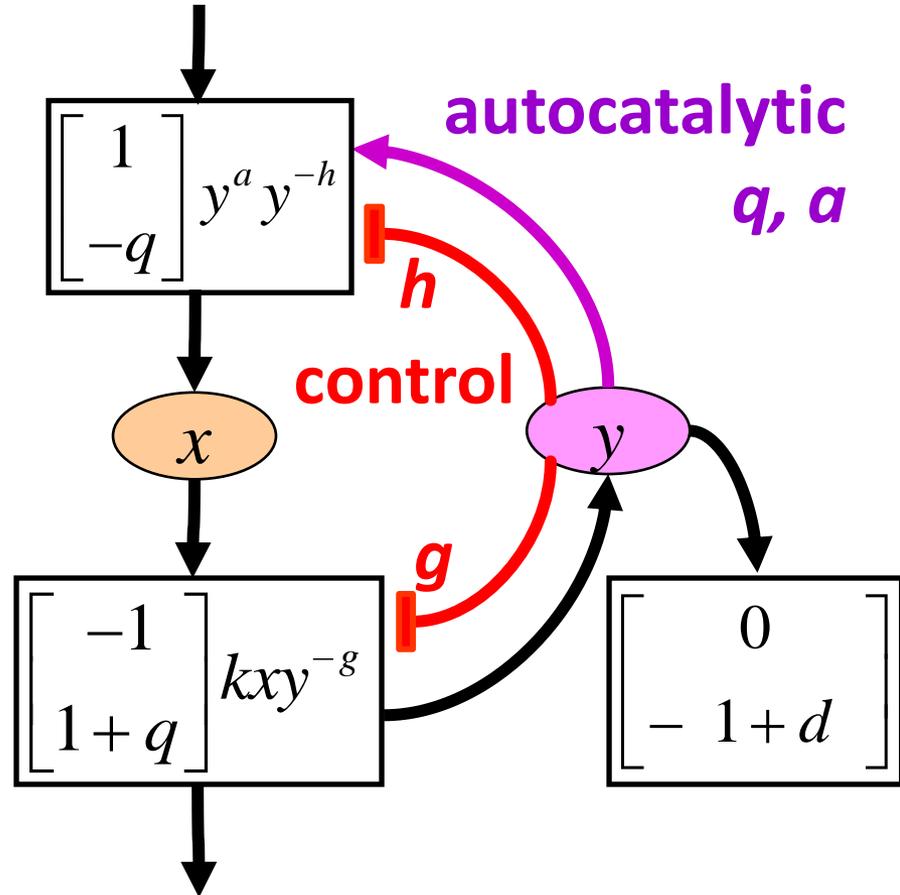
Autocatalysis necessary

Less AutoC \approx more overhead

Stoichiometry q

Rate exponent a

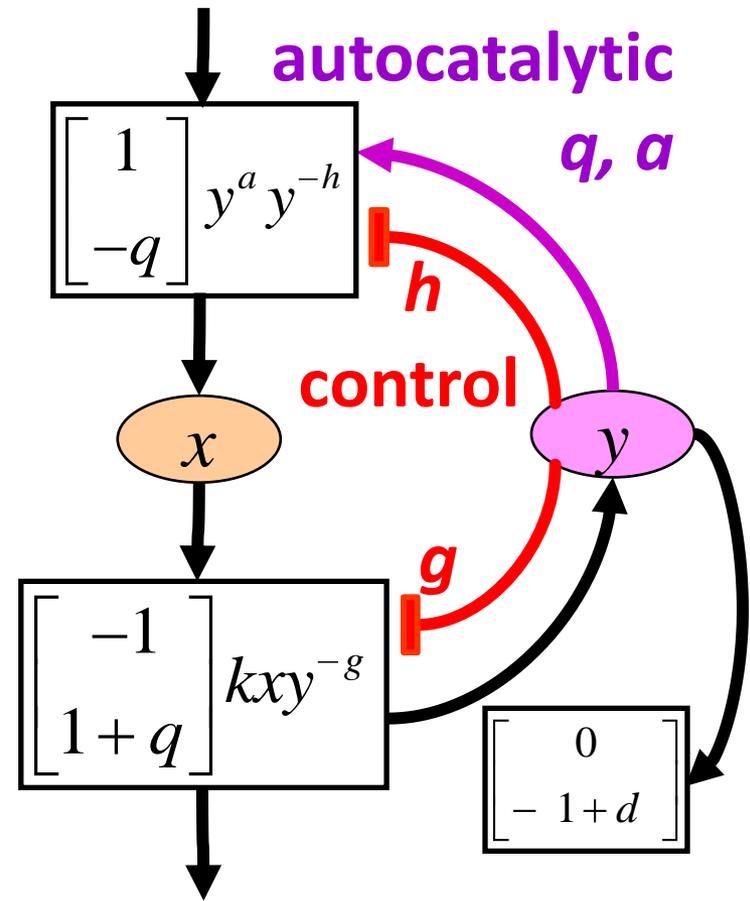
(WT $q=a=1$)



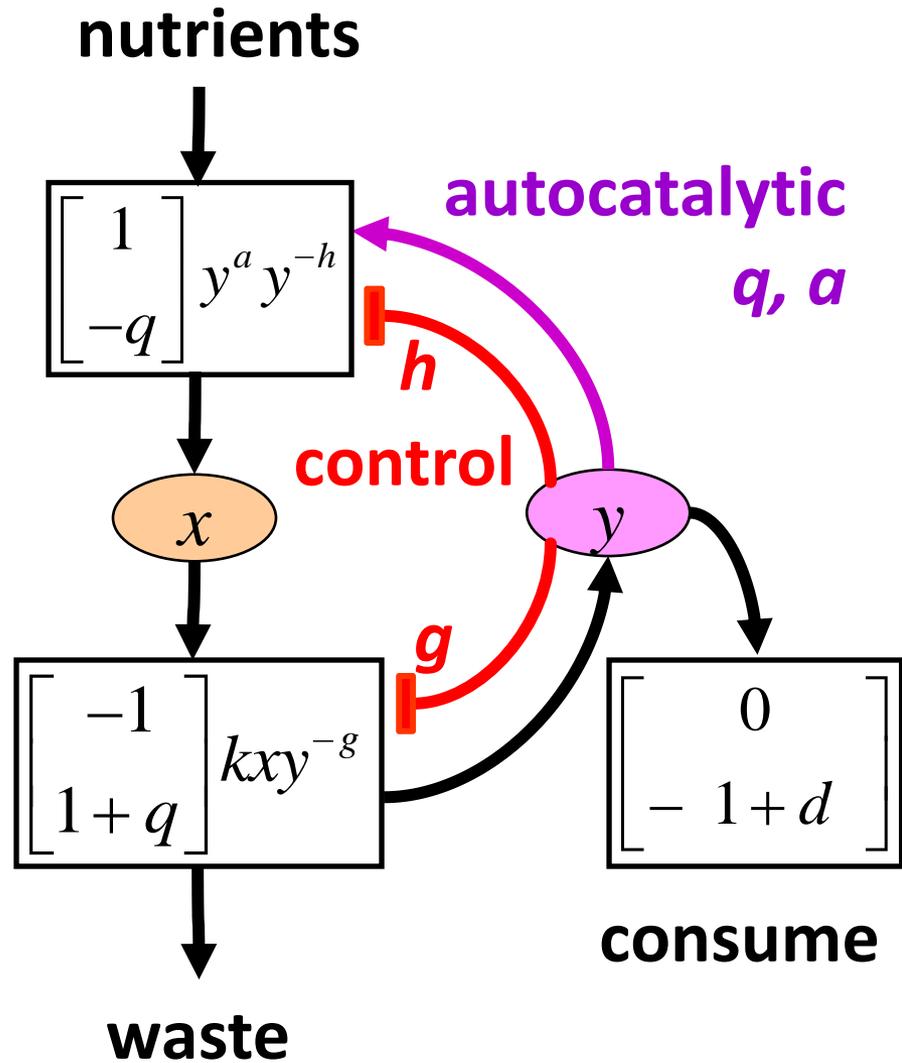
	h	g	k	q	a
↑Complexity	↑	↑		↑	↑

↑Overhead	↑	↑	↑	↓	↓
↑Enzyme size	↑	↑	↑		
↑Enzyme #			↑		
Autocatalysis				↓	↓

	h	g	k	q	a
Expensive	↑	↑	↑	↕	↕



- Fragility/Robustness
 - Disturbance rejection
 - Stability



Steady state

$$\Rightarrow \bar{y}^a \bar{y}^{-h} = k\bar{x}\bar{y}^{-g} = 1 + \bar{d}$$

$$d = 0 \Rightarrow \bar{y} = k\bar{x} = 1$$

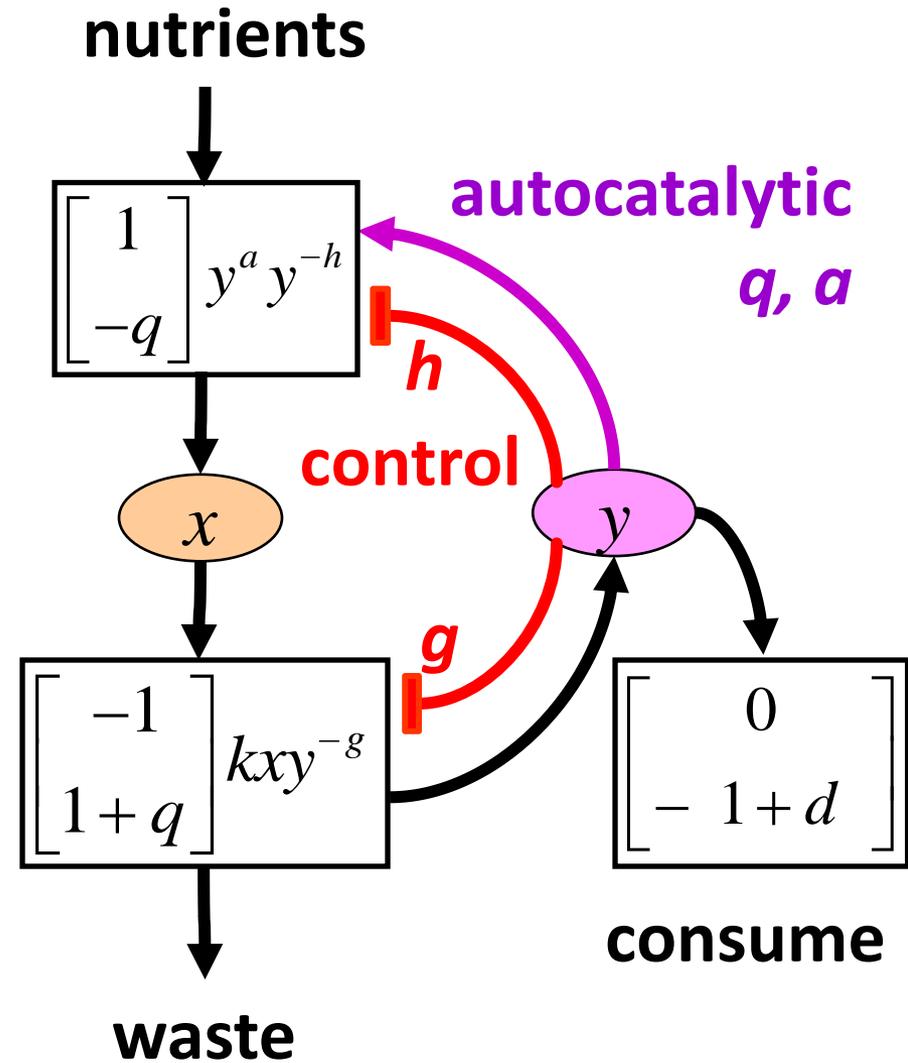
$$0 = \begin{bmatrix} 1 \\ -q \end{bmatrix} \bar{y}^a \bar{y}^{-h}$$

$$+ \begin{bmatrix} -1 \\ 1+q \end{bmatrix} k\bar{x}\bar{y}^{-g} + \begin{bmatrix} 0 \\ -1+\bar{d} \end{bmatrix}$$

Linearize

$$\frac{d}{dt} \begin{bmatrix} \Delta x \\ \Delta y \end{bmatrix} = \begin{bmatrix} 1 \\ -q \end{bmatrix} a - h \Delta y$$

$$+ \begin{bmatrix} -1 \\ 1+q \end{bmatrix} k\Delta x - g\Delta y + \begin{bmatrix} 0 \\ -1 \end{bmatrix} d$$

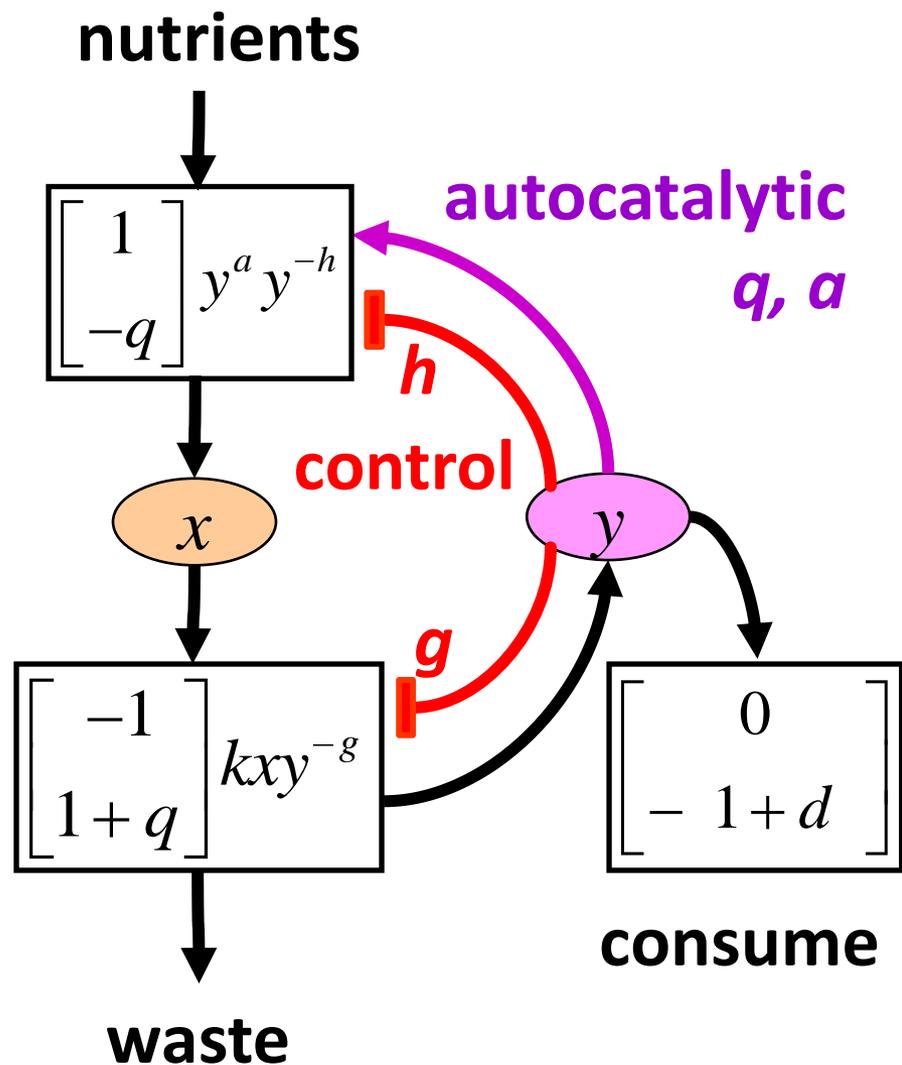


$$\frac{d}{dt} \begin{bmatrix} \Delta x \\ \Delta y \end{bmatrix} = A \begin{bmatrix} \Delta x \\ \Delta y \end{bmatrix} + \begin{bmatrix} 0 \\ -1 \end{bmatrix} d$$

$$A = \begin{bmatrix} -k & a-h+g \\ 1+q & k & -q & a-h & -1+q & g \end{bmatrix}$$

Linearize

$$\frac{d}{dt} \begin{bmatrix} \Delta x \\ \Delta y \end{bmatrix} = \begin{bmatrix} 1 \\ -q \end{bmatrix} a-h \Delta y + \begin{bmatrix} -1 \\ 1+q \end{bmatrix} k\Delta x - g\Delta y + \begin{bmatrix} 0 \\ -1 \end{bmatrix} d$$



$$\frac{d}{dt} \begin{bmatrix} \Delta x \\ \Delta y \end{bmatrix} = A \begin{bmatrix} \Delta x \\ \Delta y \end{bmatrix} + \begin{bmatrix} 0 \\ -1 \end{bmatrix} d$$

$$A = \begin{bmatrix} -k & & & a-h+g & & \\ & 1+q & k & -q & a-h & -1+q & g \\ & & & & & & \end{bmatrix}$$

Disturbance response

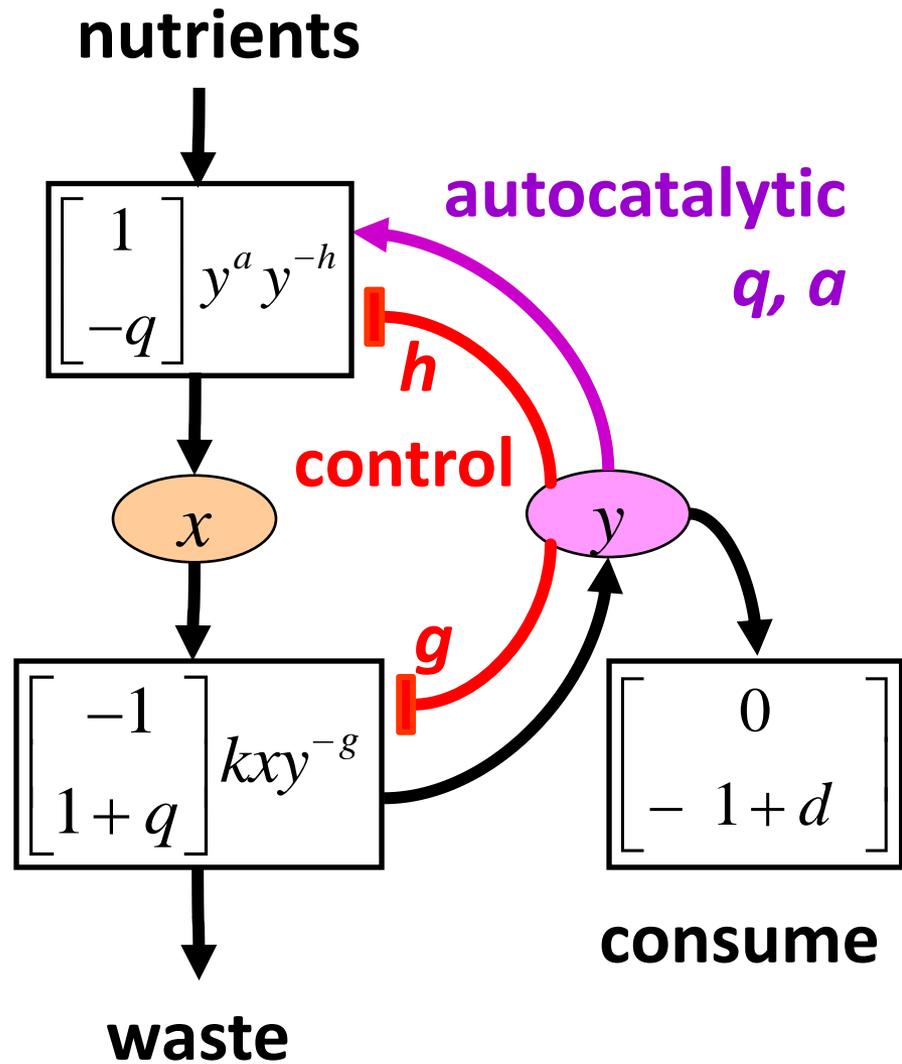
$$\left| \frac{\Delta \bar{y}}{\bar{d}} \right| \square \left| \frac{\bar{y} - 1}{\bar{d}} \right| = \left| \frac{1}{h-a} \right|$$

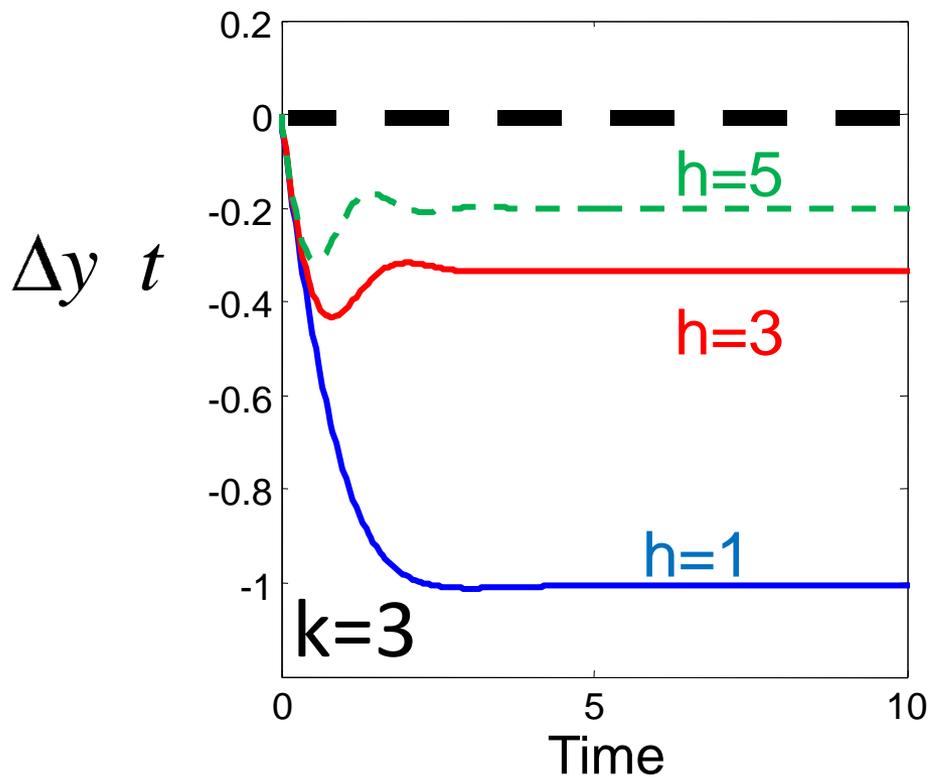
Stability

$$0 < h-a < \frac{k + 1+q}{q} g$$

Crash

Oscillate

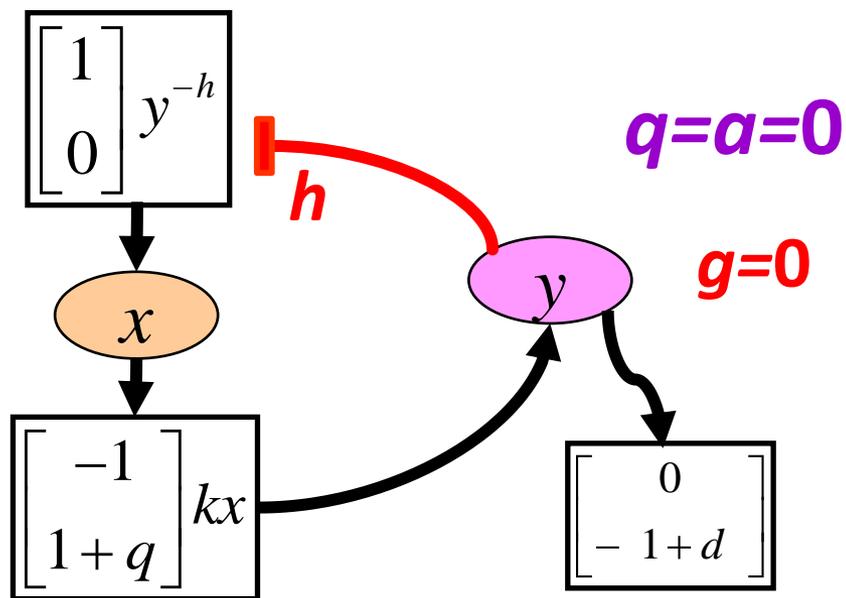




$$\left| \frac{\Delta \bar{y}}{\bar{d}} \right| \square \left| \frac{\bar{y} - 1}{\bar{d}} \right| = \left| \frac{1}{h} \right|$$

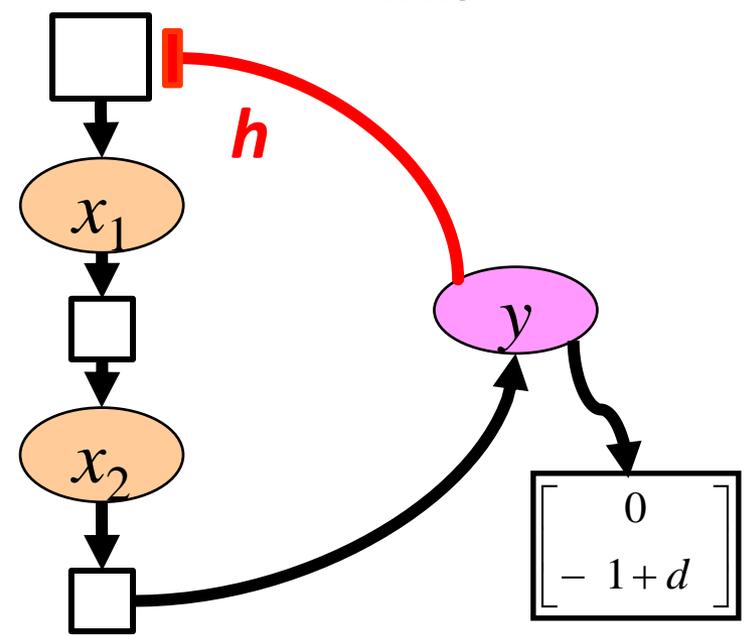
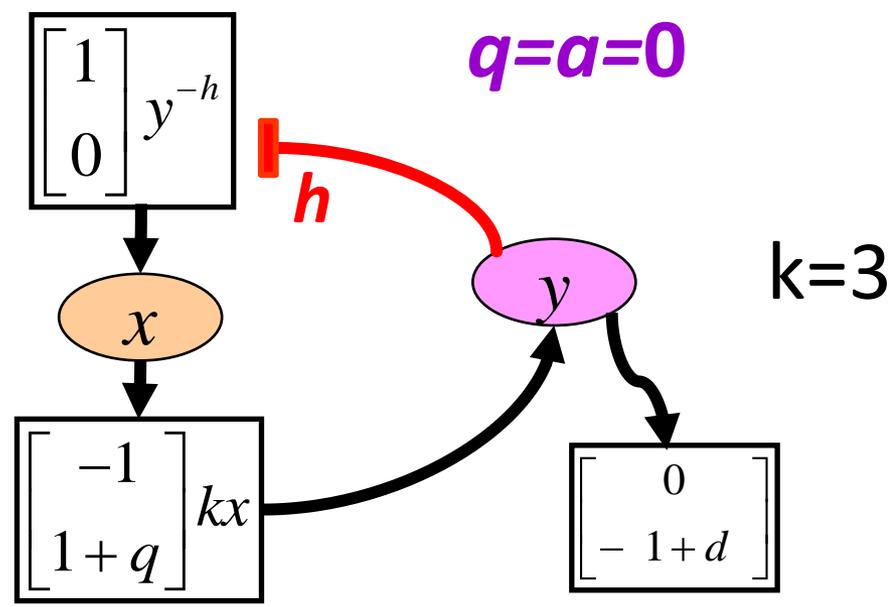
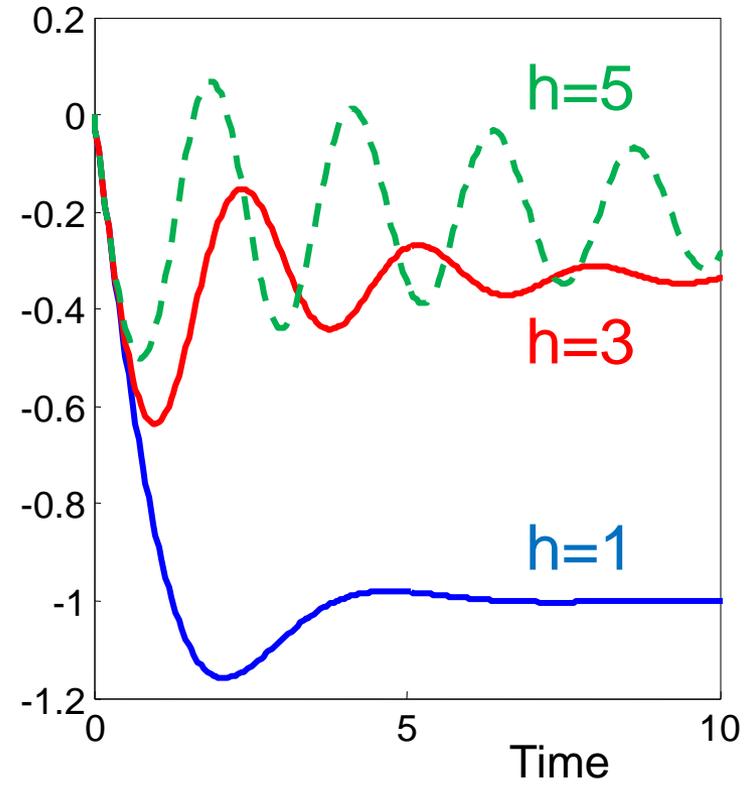
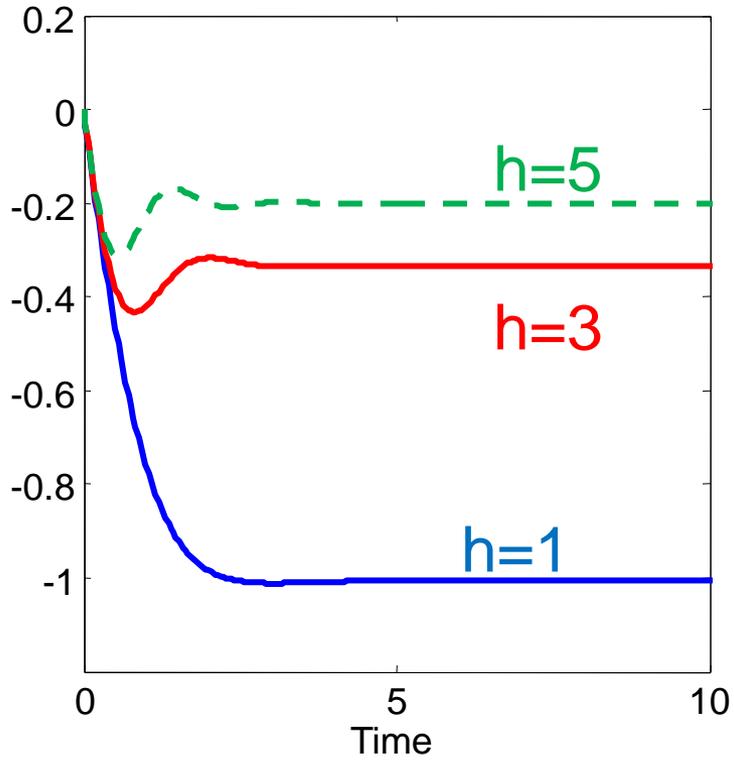
Stability

$$0 < h < \infty$$



$$A = \begin{bmatrix} -k & -h \\ k & 0 \end{bmatrix}$$

Time Simulation



Disturbance response

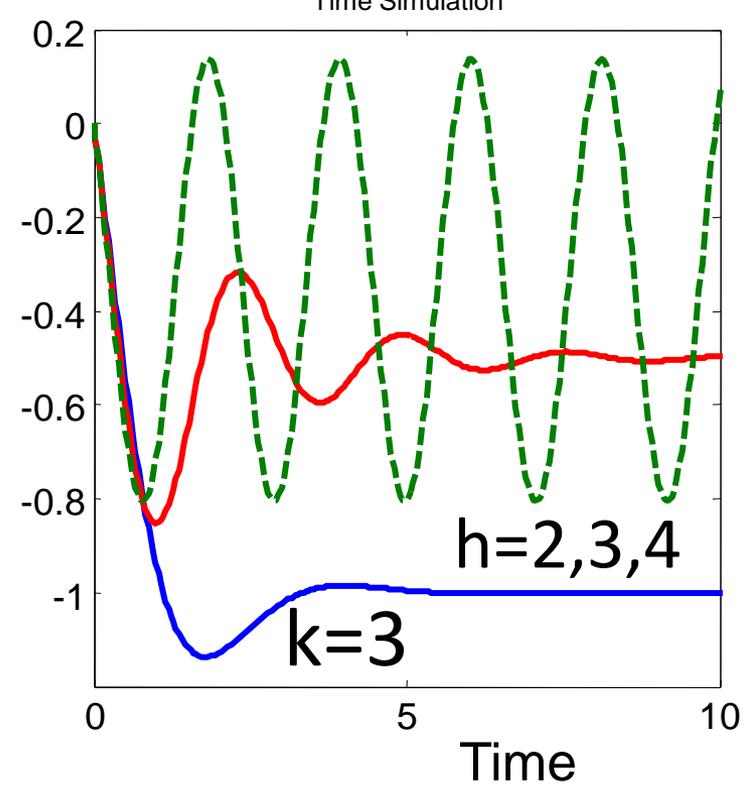
$$\left| \frac{\Delta \bar{y}}{\bar{d}} \right| = \left| \frac{1}{h-a} \right|$$

Stability

$$0 < h-a < \frac{k}{q}$$

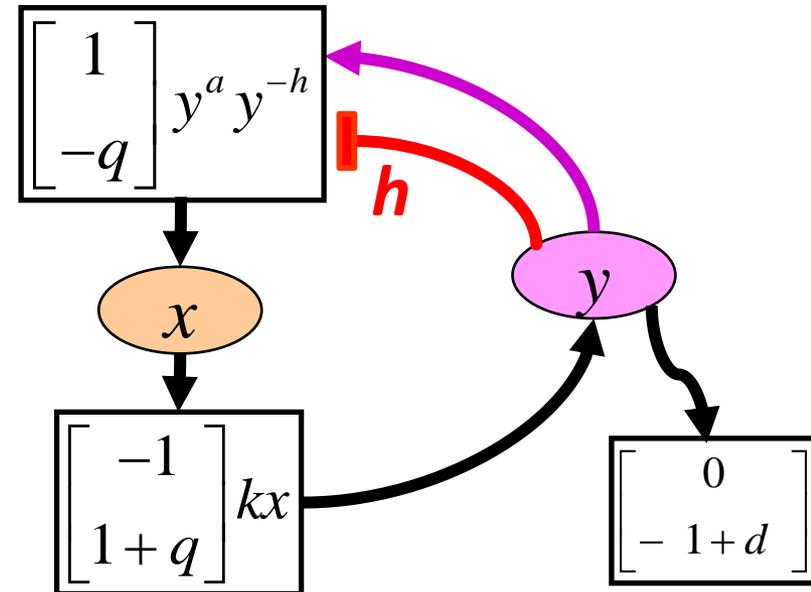
$$A = \begin{bmatrix} -k & 1-h \\ 2k & -1-h \end{bmatrix}$$

Δy t

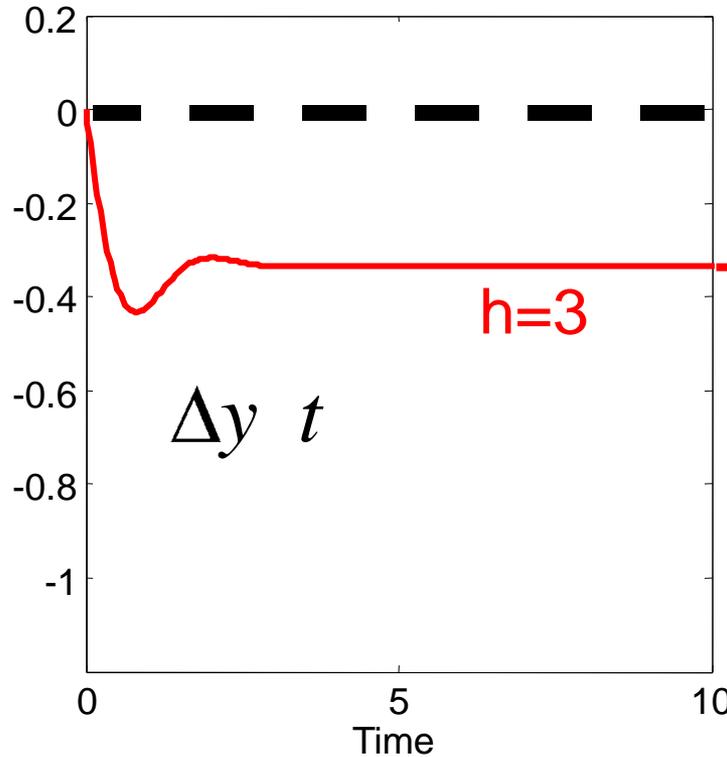


$q=a=1$

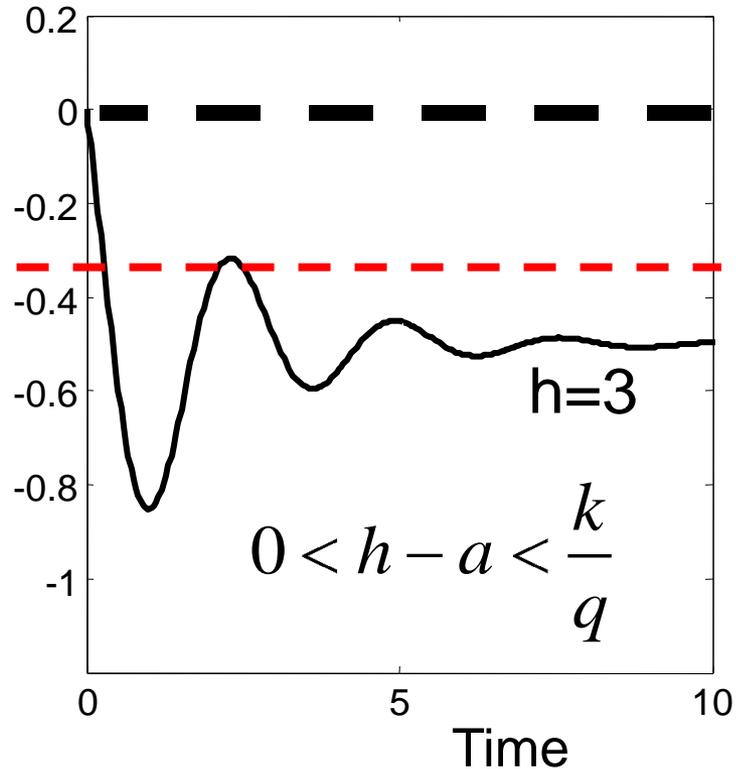
$g=0$



Time Simulation

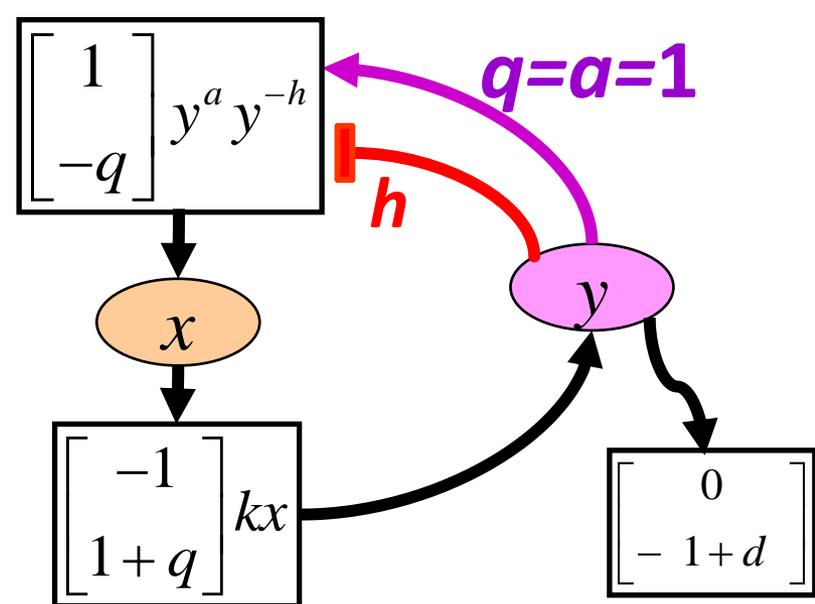
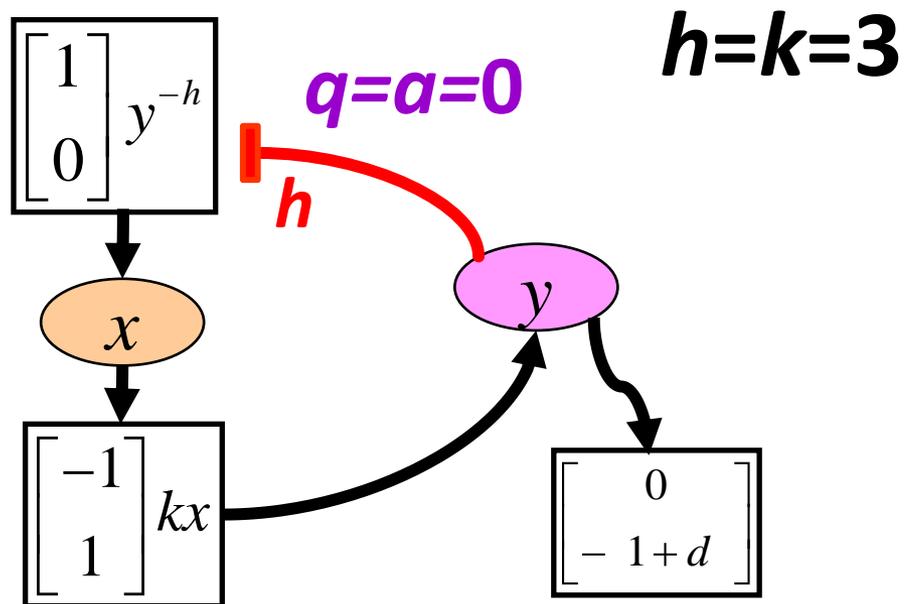


Time Simulation



Ideal

$$|\Delta \bar{y}| = \left| \frac{1}{h-a} \right|$$

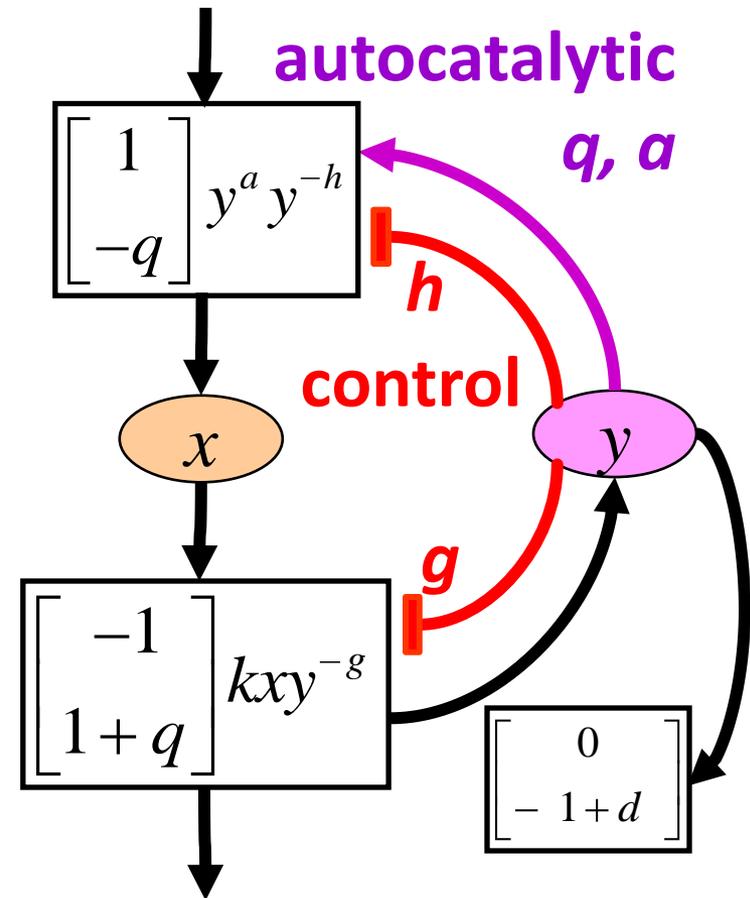


Quantify tradeoffs

(x, y, d) = signals

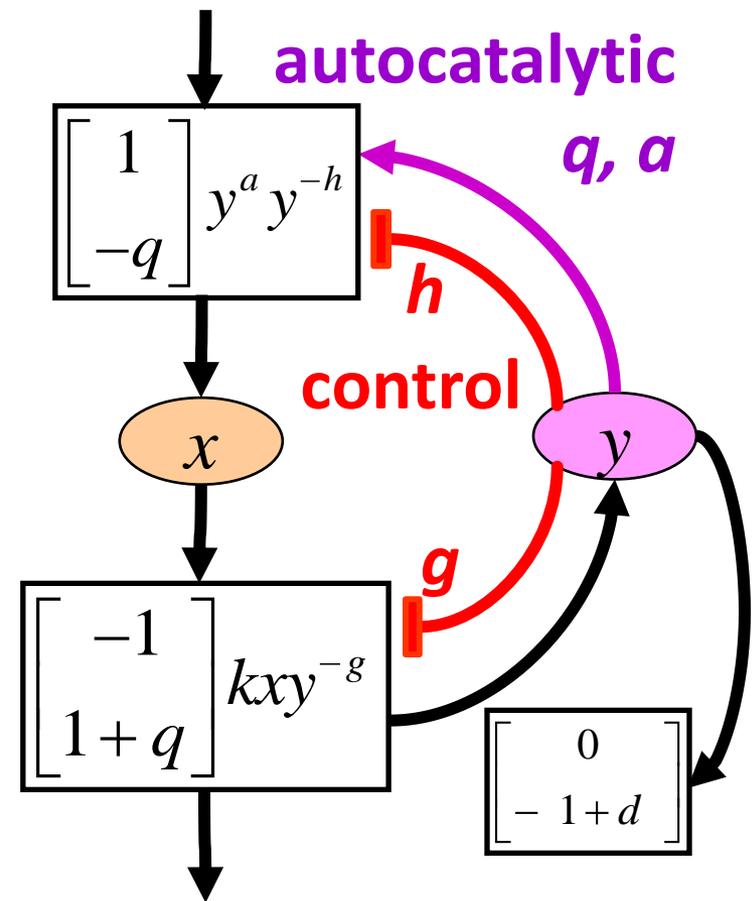
(q, a, k, h, g) = “constants”

- Complexity
 - Enzymes
 - Network
- Metabolic Overhead
 - Enzyme size
 - Enzyme amount
 - Autocatalysis
- Fragility
 - Disturbance
 - Stability



	h	g	k	q	a
↑Complexity	↑	↑		↑	↑
↑Overhead	↑	↑	↑	↓	↓
↑Enzyme size	↑	↑	↑		
↑Enzyme #			↑		
Autocatalysis				↓	↓
↑Fragile/dist.	↓				↑
↑Fragile/oscill.	↑	↓	↓	↑	

Expensive	↕	↕	↕	↕	↕
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Disturbance response

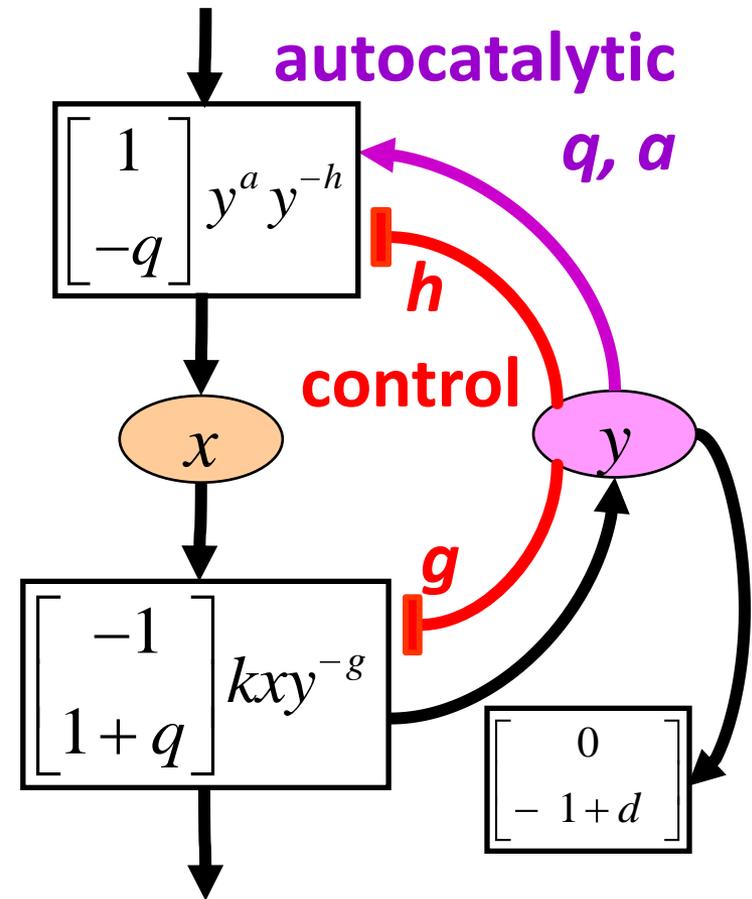
$$\left| \frac{\Delta \bar{y}}{\bar{d}} \right| \square \left| \frac{1}{h-a} \right|$$

Stability

$$0 < h - a < \frac{k + 1 + q}{q} g$$

	h	g	k	q	a
↑Complexity	↑	↑		↑	↑
↑Overhead	↑	↑	↑	↓	↓
↑Enzyme size	↑	↑	↑		
↑Enzyme #			↑		
Autocatalysis				↓	↓
↑Fragile/dist.	↓				↑
↑Fragile/oscill.	↑	↓	↓	↑	

Expensive	↕	↕	↕	↕	↕
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Disturbance response

$$\left| \frac{\Delta \bar{y}}{\bar{d}} \right| \square \left| \frac{1}{h-a} \right|$$

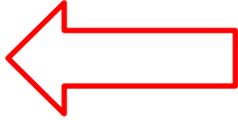
Stability

$$0 < h - a < \frac{k + 1 + q}{q} g$$

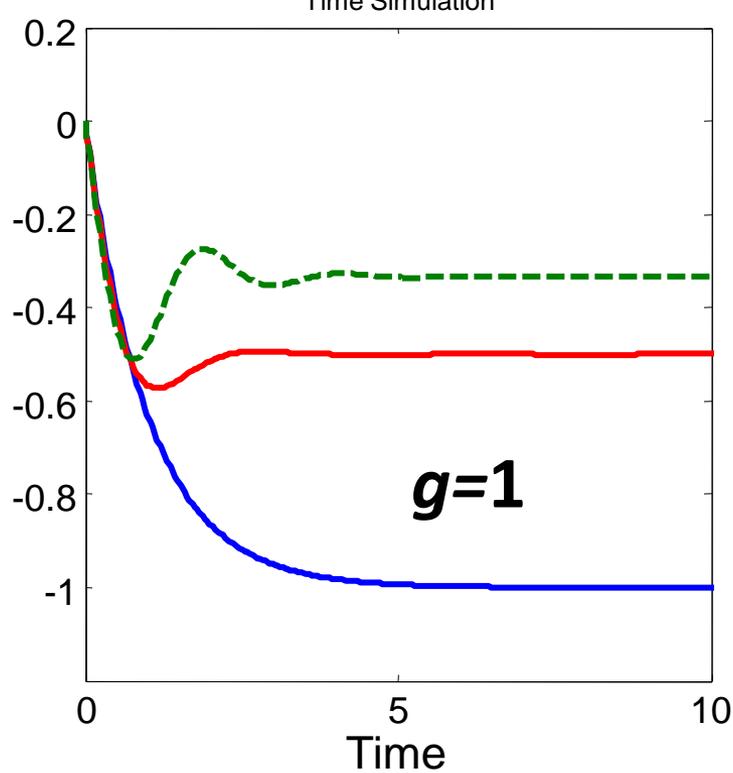
Disturbance

$$\left| \frac{\Delta \bar{y}}{\bar{d}} \right| < \left| \frac{1}{h-a} \right| > \frac{q}{k+1+qg}$$

- Hard limit
- Boundary is oscillatory
- $g > 0$ helps

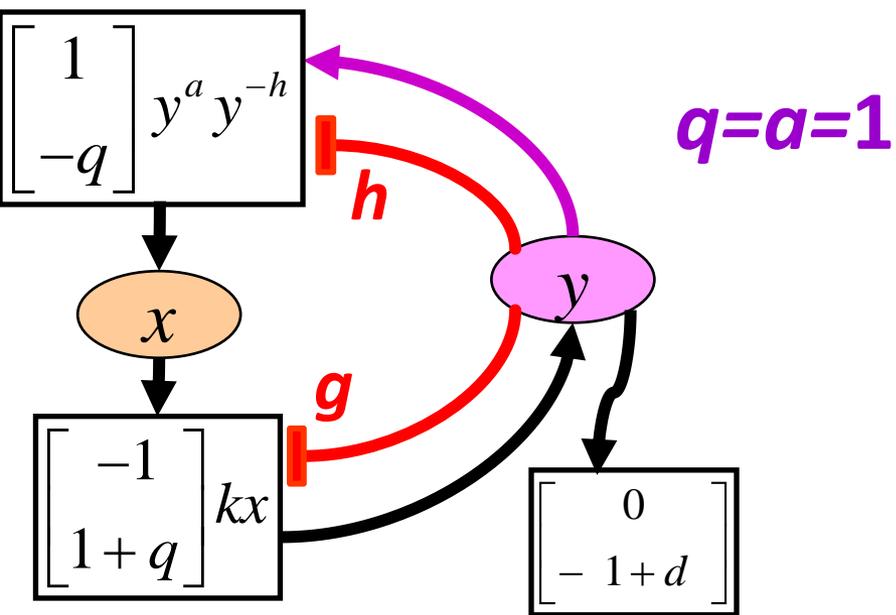
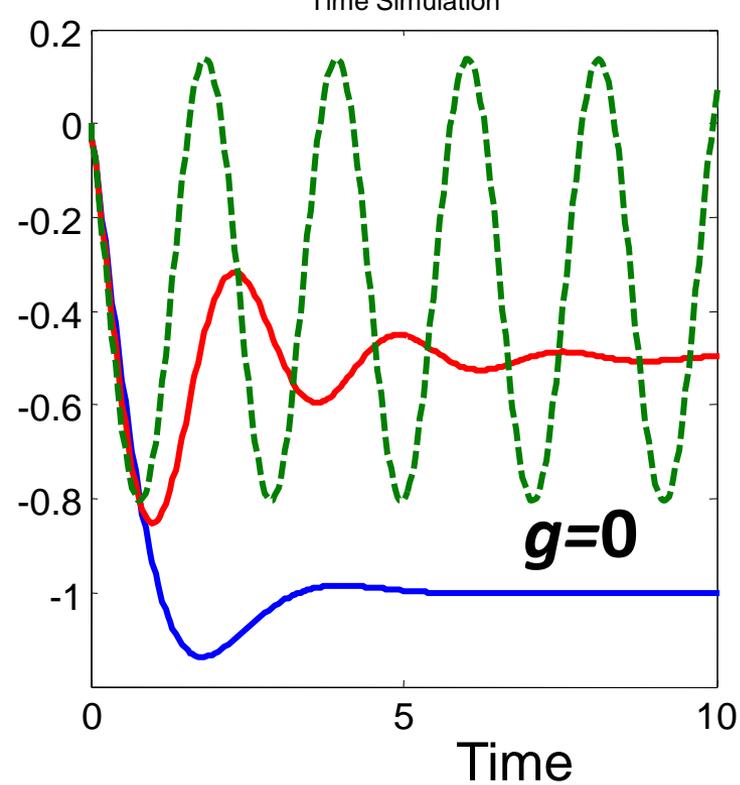

$$0 < h-a < \frac{k+1+qg}{q}$$

Stability



$\Delta y \quad t$

$h=2,3,4$
 $k=3$

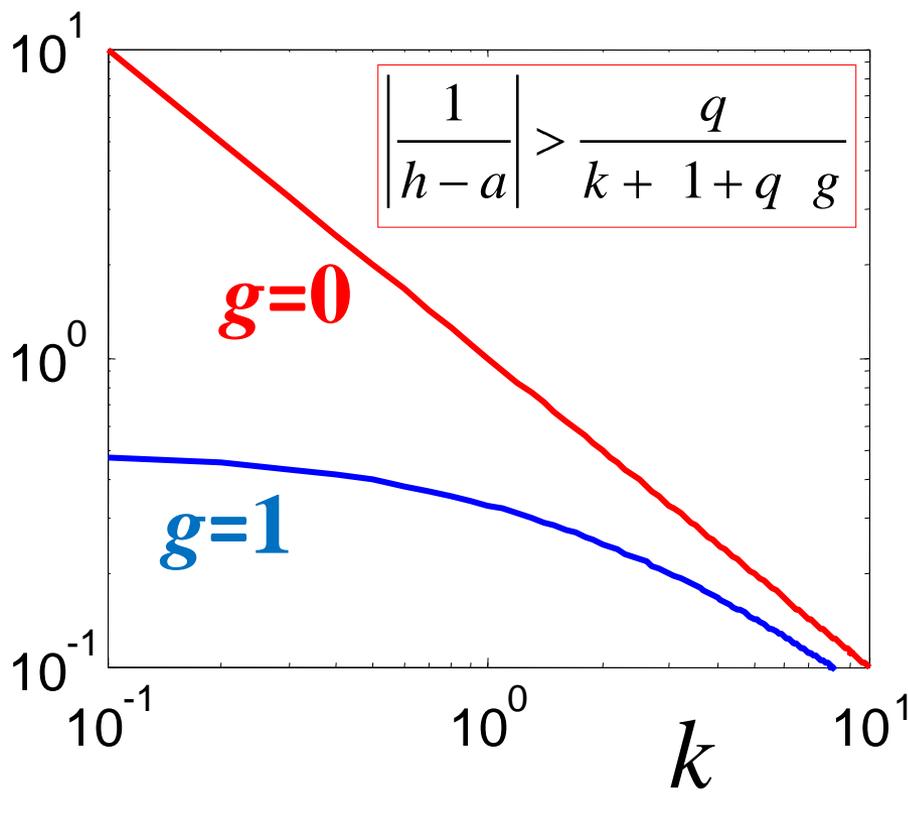


- Hard limit
- Boundary is oscillatory
- $g > 0$ helps

$$\left| \frac{\Delta \bar{y}}{\bar{d}} \right| \leq \left| \frac{1}{h-a} \right| > \frac{q}{k+1+qg}$$

Fragility

$$\left| \frac{1}{h-a} \right|$$



Cheap &
Robust

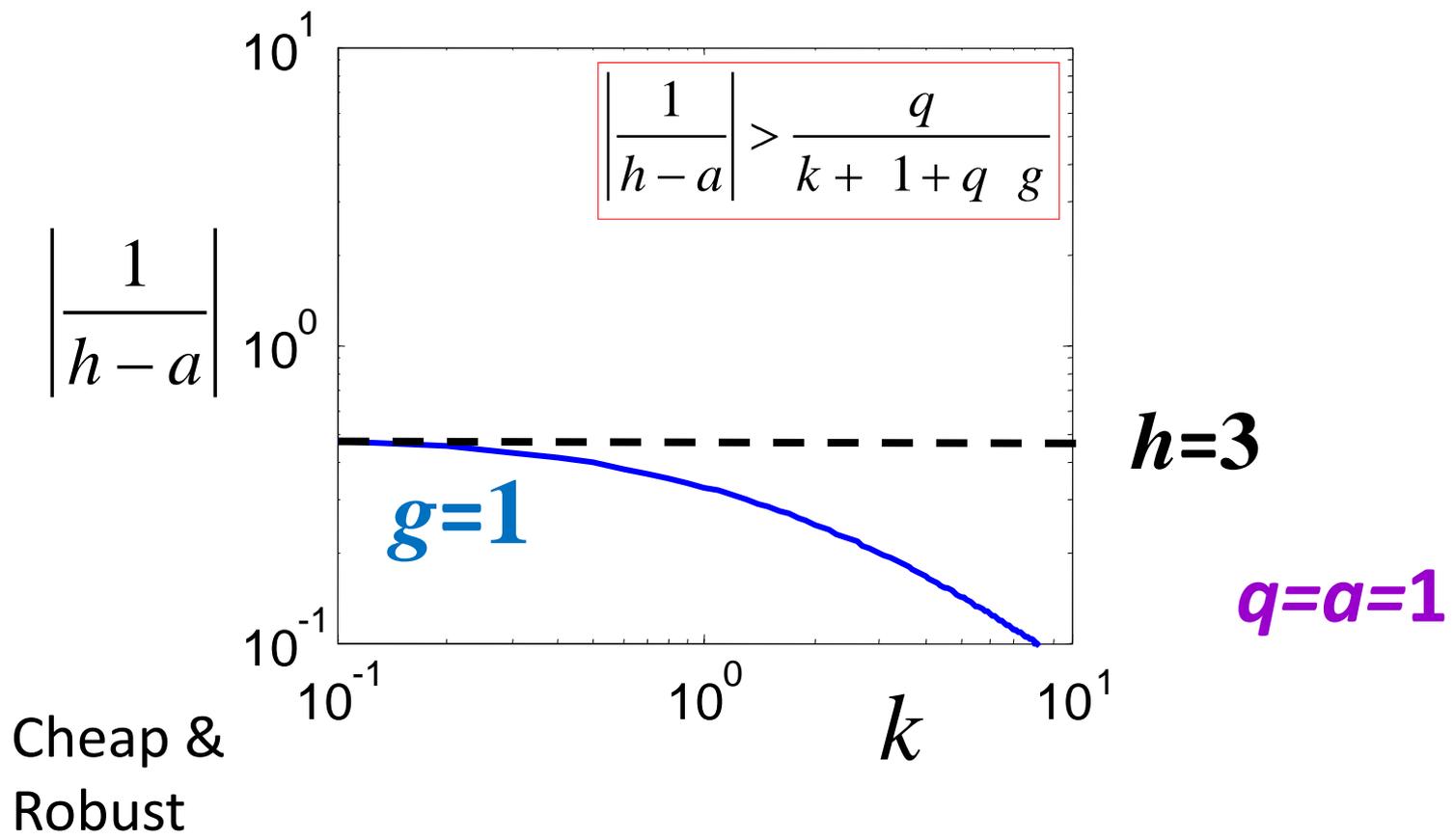
Overhead

Disturbance

$$\left| \frac{\Delta \bar{y}}{\bar{d}} \right| \square \left| \frac{1}{h-a} \right| > \frac{q}{k+1+qg}$$

- Hard limit
- Boundary is oscillatory
- $g > 0$ helps

← $0 < h-a < \frac{k+1+qg}{q}$
Stability



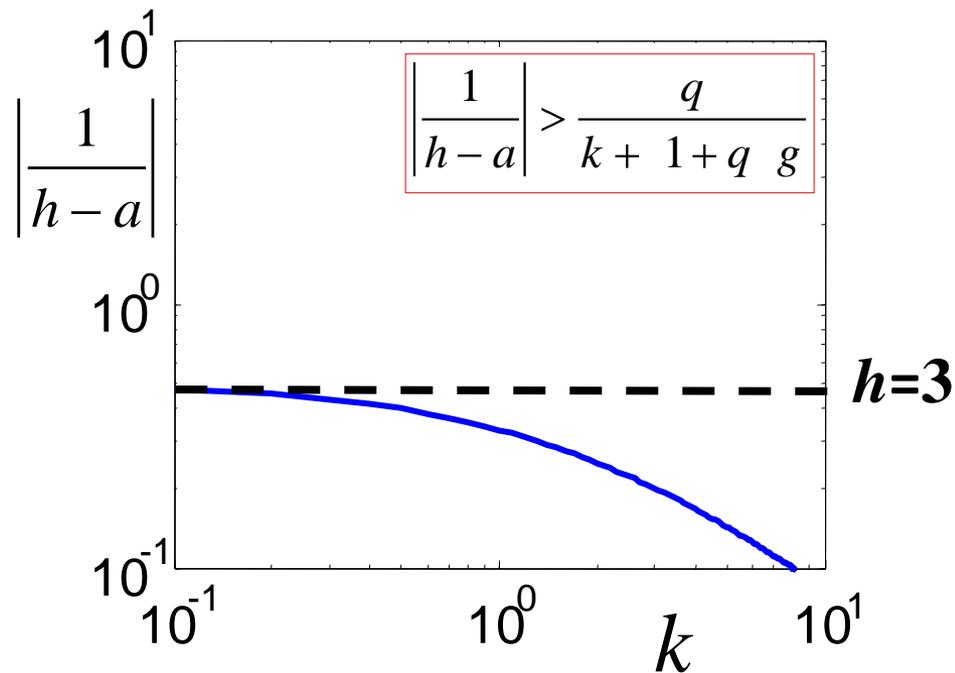
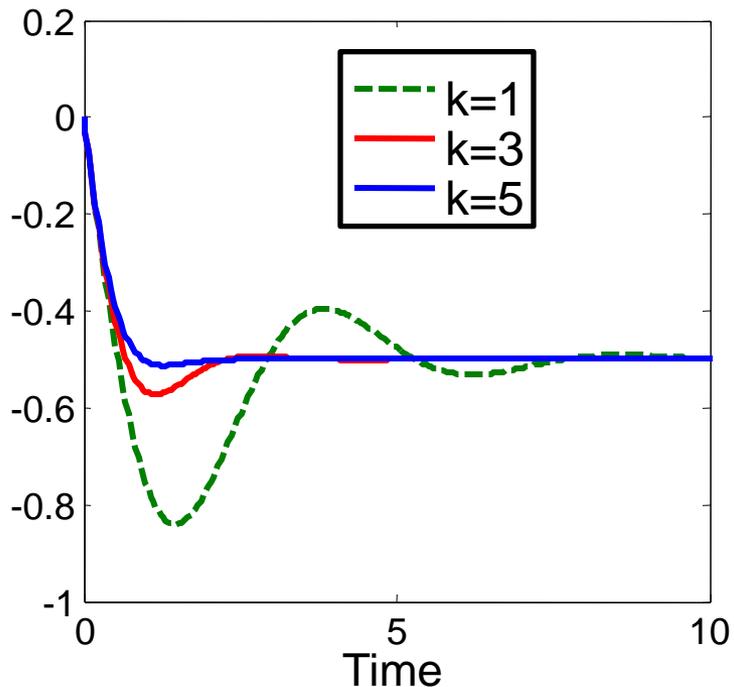
$q=a=1$
 $h=3$
 $g=1$
 stable for all $k>0$
 $0 < 2 < k+2$

Disturbance

$$\left| \frac{\Delta \bar{y}}{\bar{d}} \right| \leq \left| \frac{1}{2} \right| > \frac{1}{k+2}$$

$0 < h-a < \frac{k+1+qg}{q}$
 Stability

Time Simulation



Disturbance

$$\left| \frac{\Delta \bar{y}}{\bar{d}} \right| \leq \left| \frac{1}{2} \right| > \frac{1}{k+2}$$

$q=a=1$

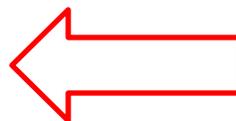
$h=3$

$g=1$



stable for all $k > 0$

$$0 < 2 < k + 2$$



$$0 < h - a < \frac{k + 1 + qg}{q}$$

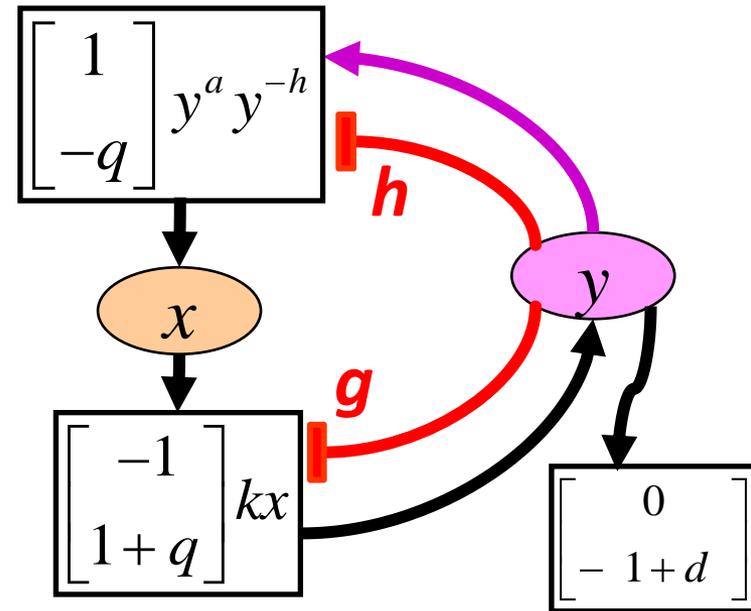
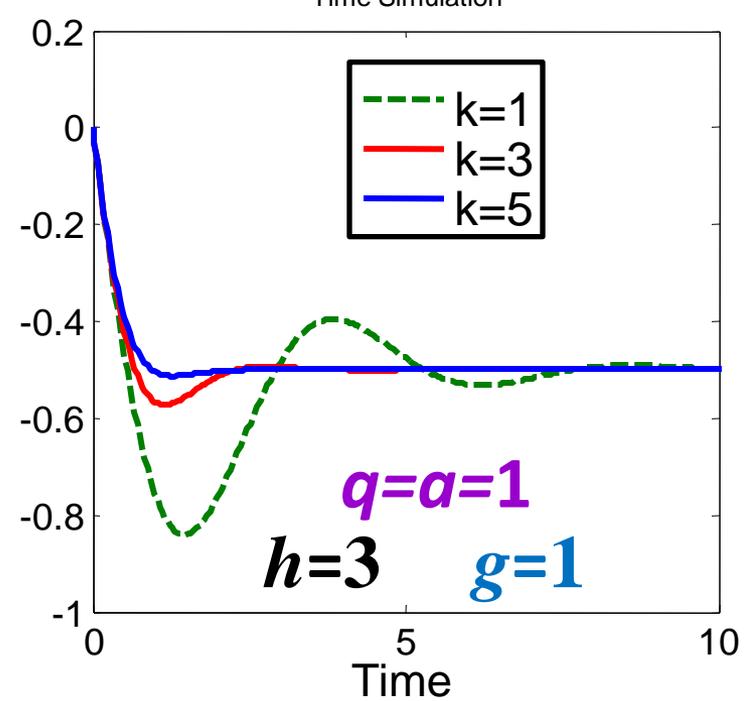
Stability

	h	g	k	q	a
↑Complexity	↑	↑		↑	↑
↑Overhead	↑	↑	↑	↓	↓
↑Enzyme size	↑	↑	↑		
↑Enzyme #			↑		
Autocatalysis				↓	↓

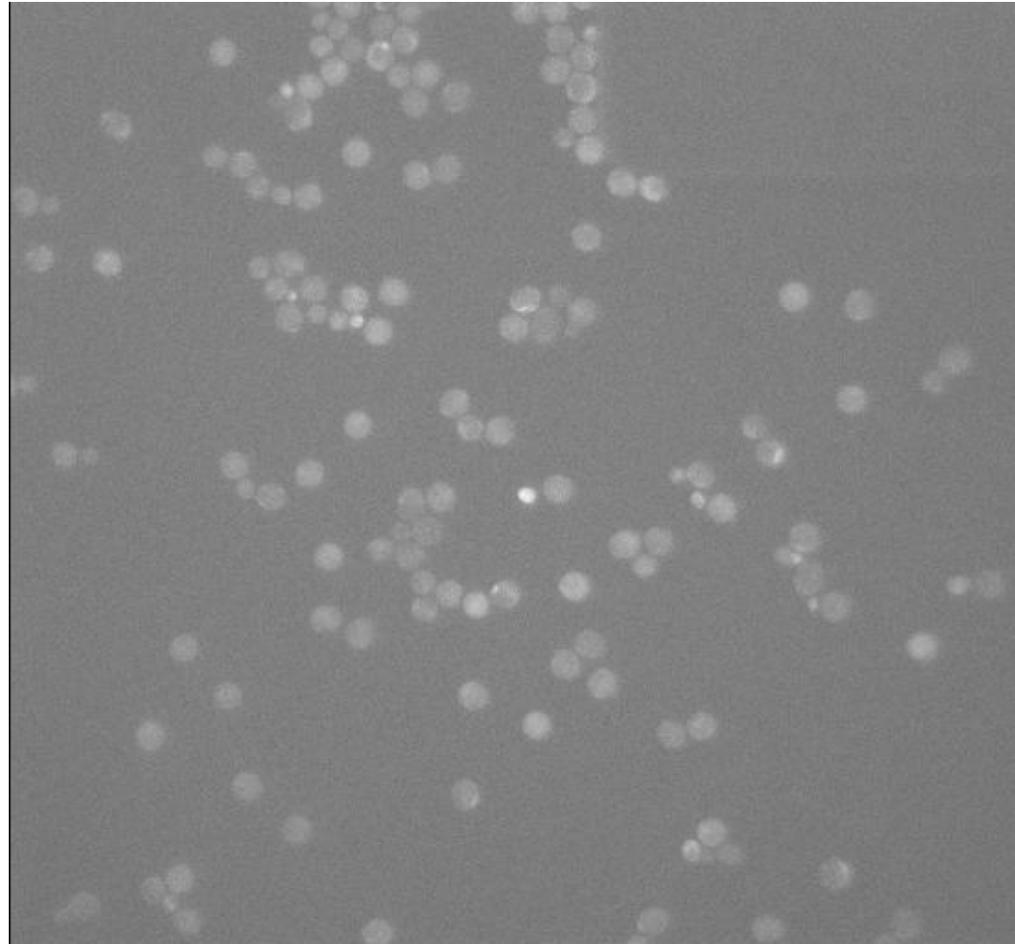
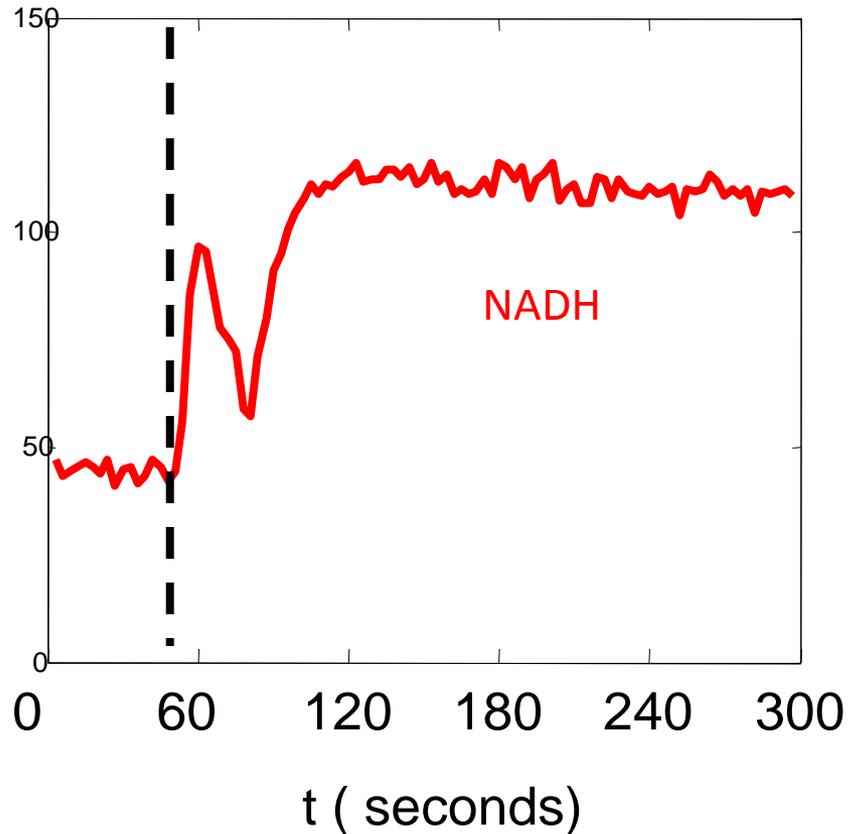
↑Fragile/dist.	↓				↑
↑Fragile/oscill.	↑	↓	↓	↑	

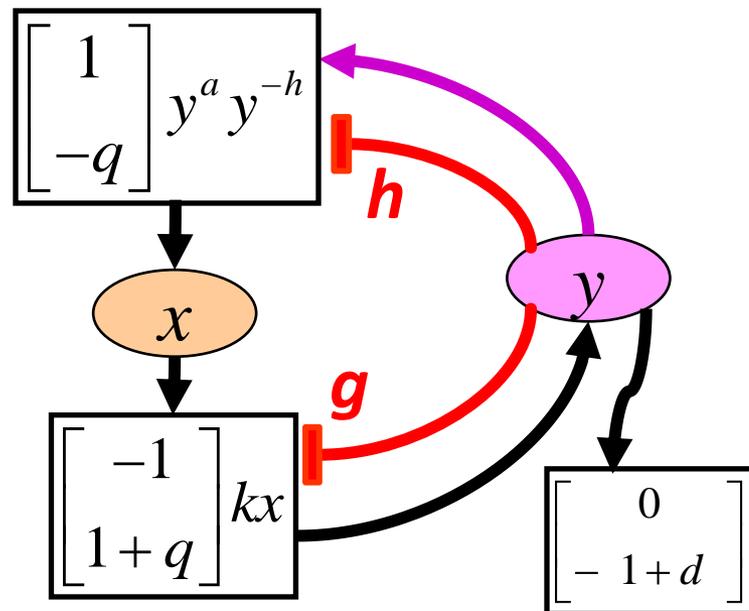
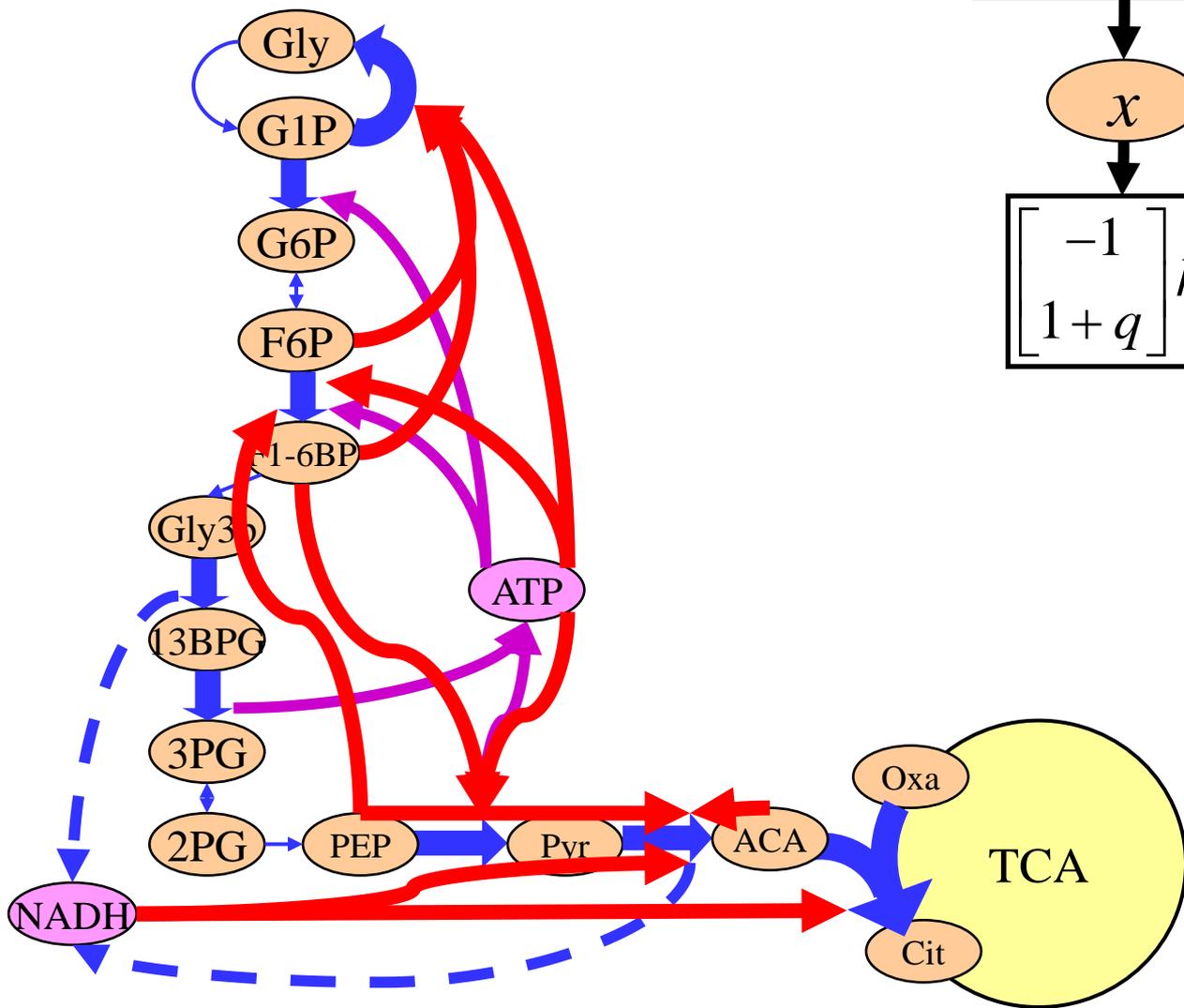
Accident or *necessity*?

$$\left| \frac{\Delta \bar{y}}{\bar{d}} \right| \square \left| \frac{1}{h-a} \right| > \frac{q}{k+1+q} \frac{1}{g}$$



- Microfluidic experiments
- Yeast strain W303 grown in Ethanol
- Glucose and KCN added → anaerobic glycolysis
- NADH measured every 3 s





	h	g	k	q	a
↑Complexity	↑	↑		↑	↑
↑Overhead	↑	↑	↑	↓	↓
↑Enzyme size	↑	↑	↑		
↑Enzyme #			↑		
Autocatalysis				↓	↓

↑Fragile/dist.	↓				↑
↑Fragile/oscill.	↑	↓	↓	↑	

$$\left| \frac{\Delta \bar{y}}{\bar{d}} \right| \square \left| \frac{1}{h-a} \right| > \frac{q}{k + 1 + q g}$$

Phenomenological

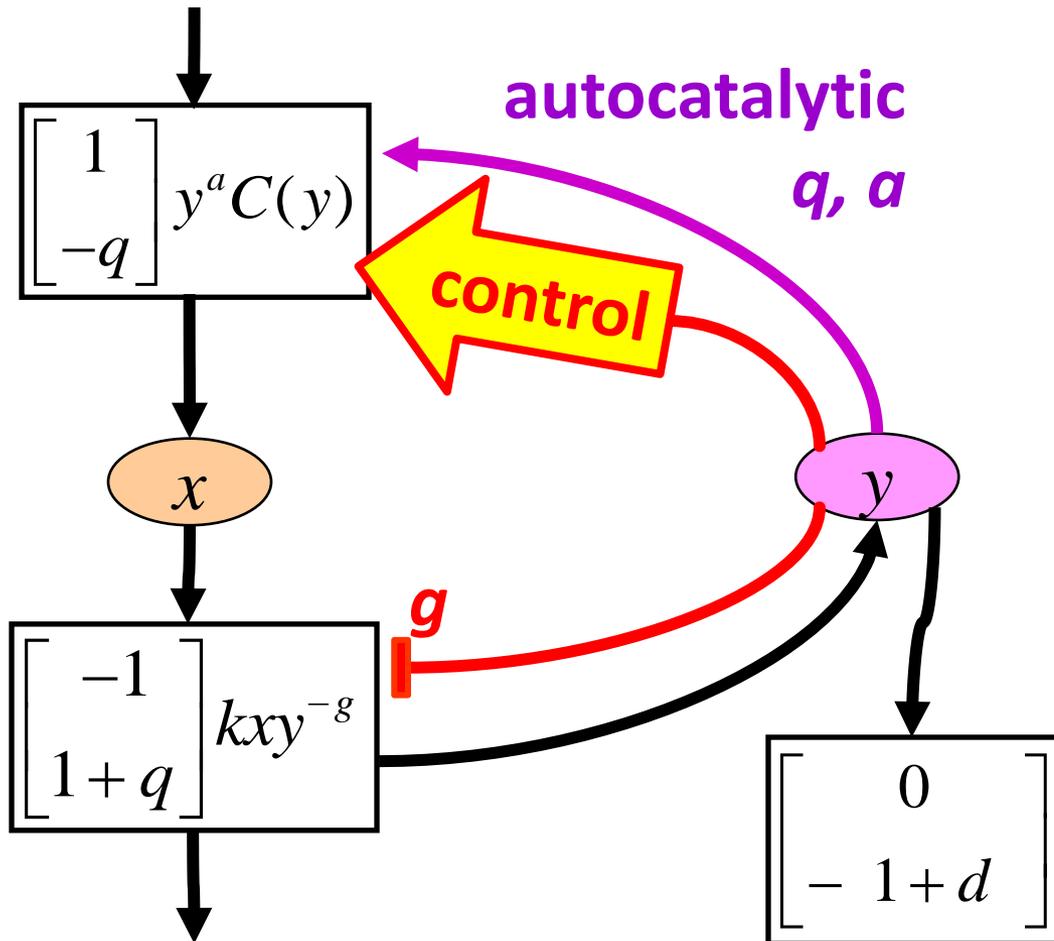
- Enzyme efficiency
- Allostery
- Autocatalysis
- Dynamics

Theory limited by

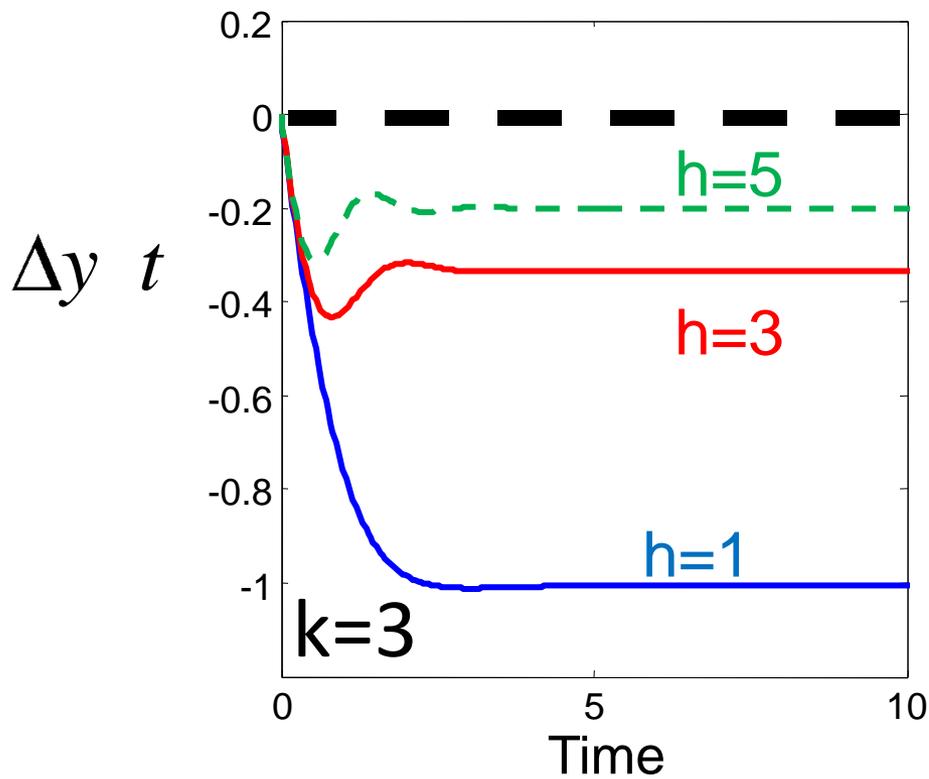
- Stat mech
- Trivial control theory

What about arbitrary

- Nonequilibrium (thermo)dynamics
- Control dynamics



What if the control *implementation* is allowed arbitrarily complex dynamics (states plus nonlinearities)?

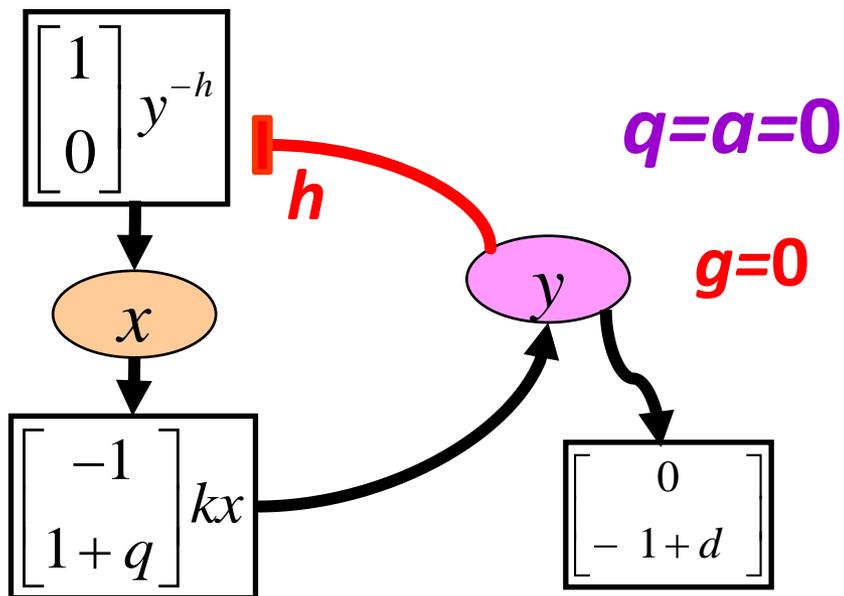


Disturbance response

$$\left| \frac{\Delta \bar{y}}{\bar{d}} \right| \square \left| \frac{\bar{y} - 1}{\bar{d}} \right| = \left| \frac{1}{h} \right|$$

Stability

$$0 < h < \infty$$



$$A = \begin{bmatrix} -k & -h \\ k & 0 \end{bmatrix}$$

Dynamic

$$WS(s) \square \frac{Y(s)}{D(s)} = 1 \quad 0 \quad sI - A \quad^{-1} \begin{bmatrix} 0 \\ -1 \end{bmatrix}$$

$$= - \left(\frac{s+k}{s^2 + (k+g+q(a-h+g))s - k(a-h)} \right)$$

Static +
stability

$$|WS \ 0| = \left| \frac{Y(0)}{D(0)} \right| = \left| \frac{\Delta \bar{y}}{\bar{d}} \right| = \left| \frac{1}{h-a} \right| > \frac{q}{k+1+qg}$$

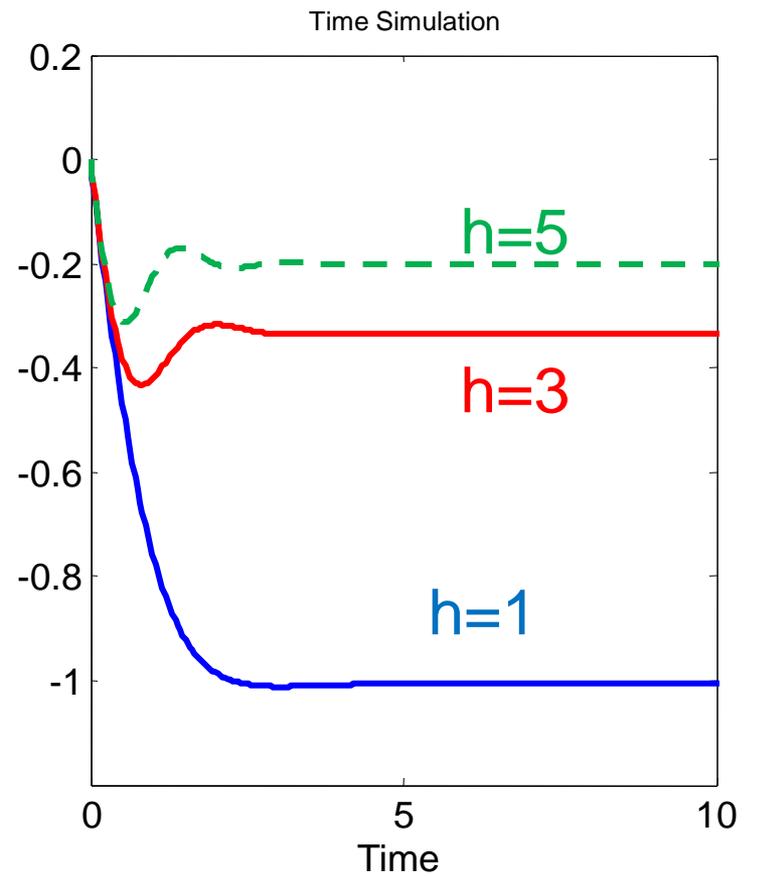
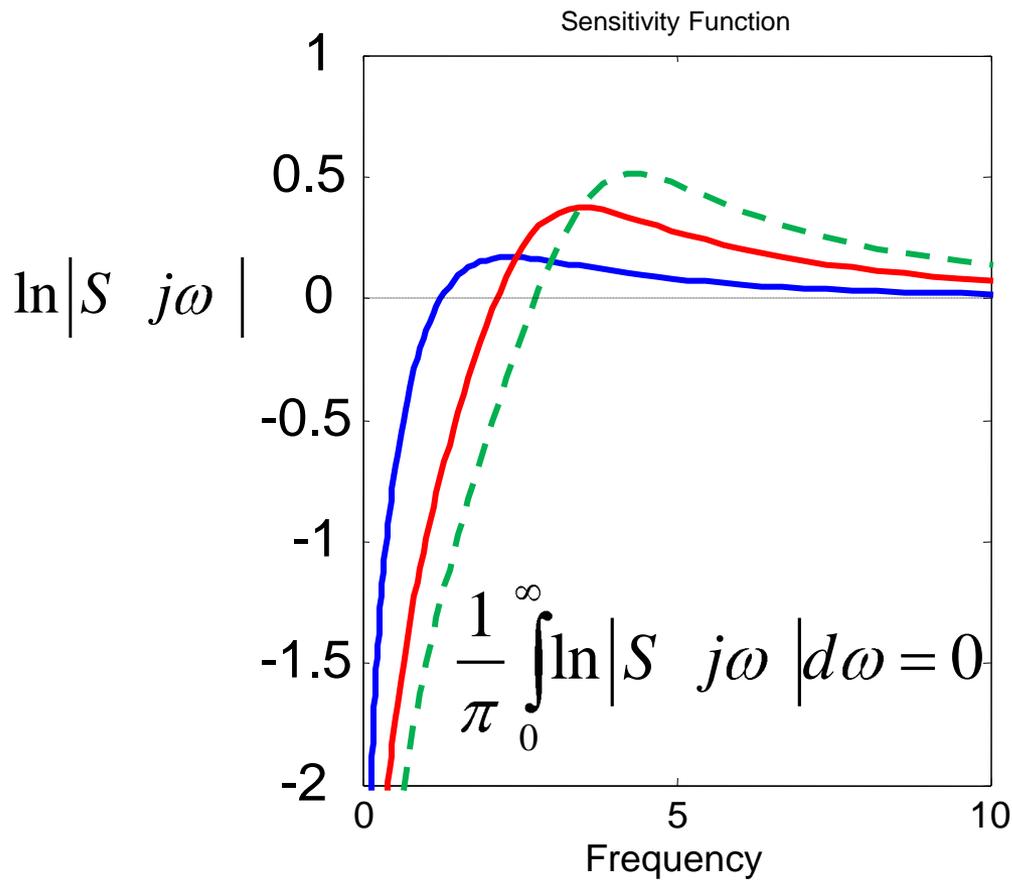
$$W \ s \square - \left(\frac{s+k}{s^2 + (k+g+q(a+g))s - ka} \right) \quad S \ s \square \left(\frac{s^2 + (k+g+q(a+g))s - ka}{s^2 + (k+g+q(a-h+g))s - k(a-h)} \right)$$

Doesn't depend on h

Does depend on h

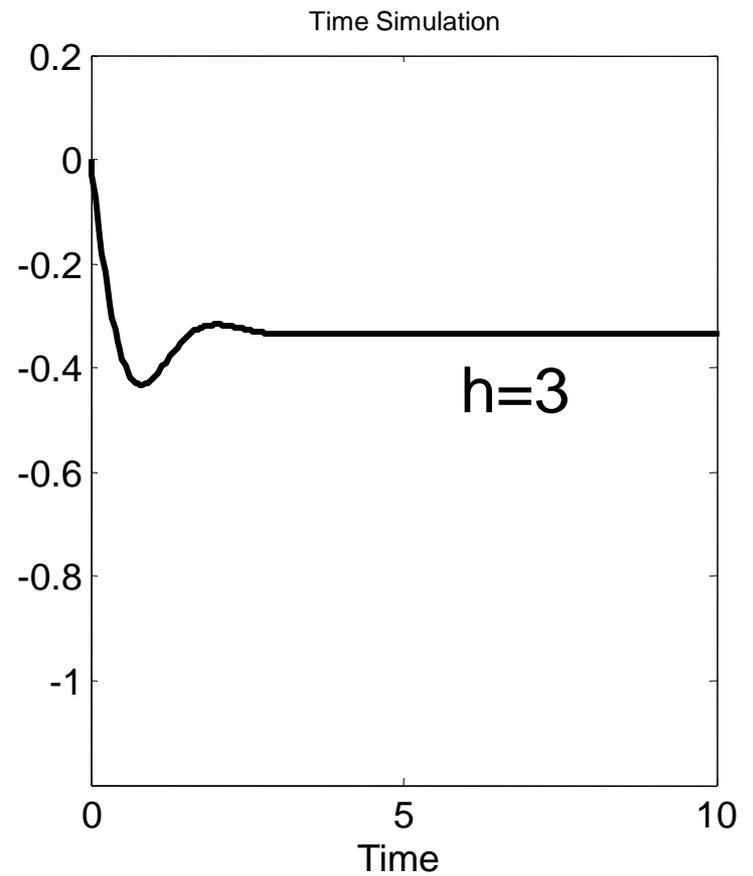
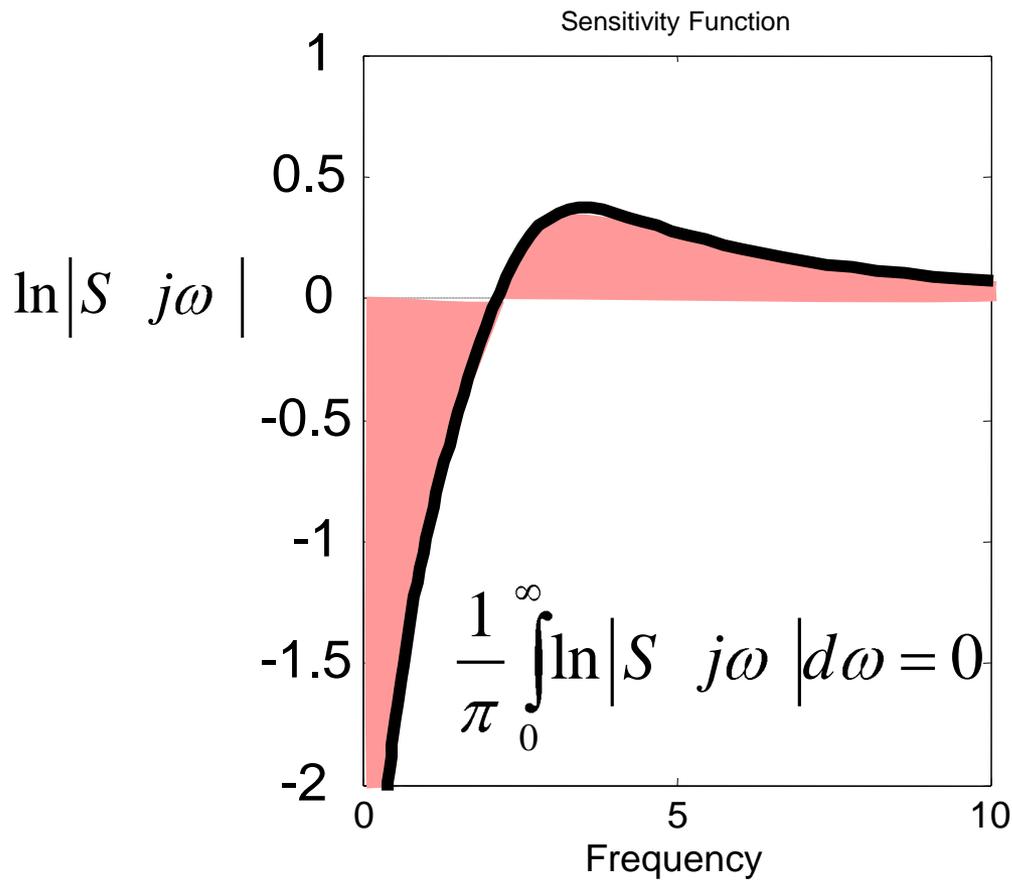
$$\text{Thm: } \frac{1}{\pi} \int_0^{\infty} \ln |S \ j\omega| \ d\omega \geq 0$$

$$\ln |WS \ j\omega| = \ln |W \ j\omega| + \ln |S \ j\omega|$$



$$\text{Thm: } \frac{1}{\pi} \int_0^{\infty} \ln|S(j\omega)| d\omega \geq 0$$

$$\ln|WS(j\omega)| = \ln|W(j\omega)| + \ln|S(j\omega)|$$



**No
matter
what!**

$$\text{Thm: } \frac{1}{\pi} \int_0^{\infty} \ln|S(j\omega)| d\omega \geq 0$$

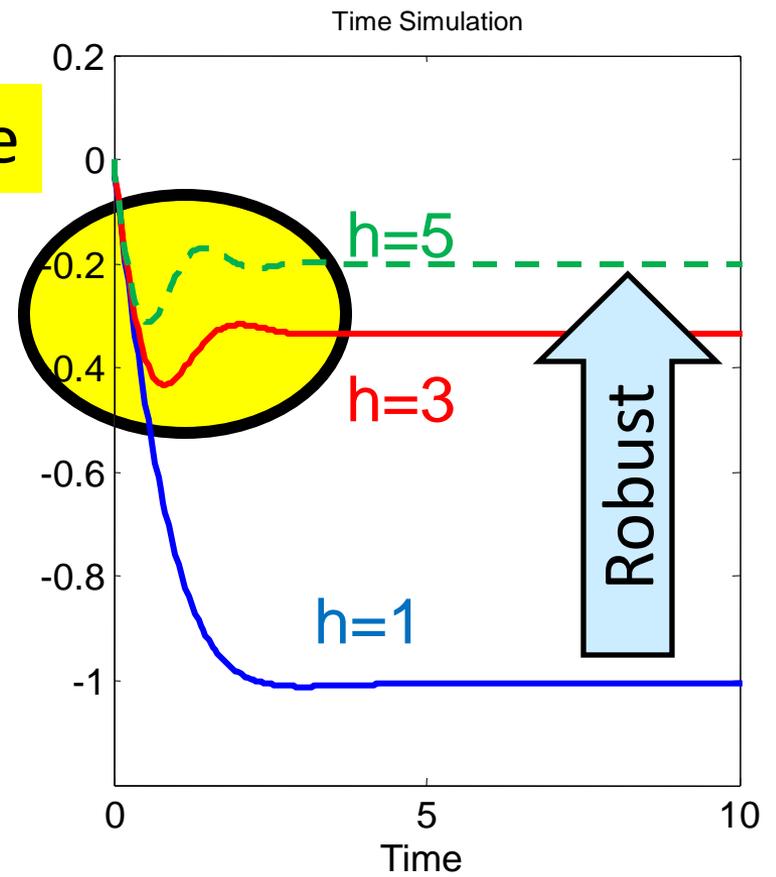
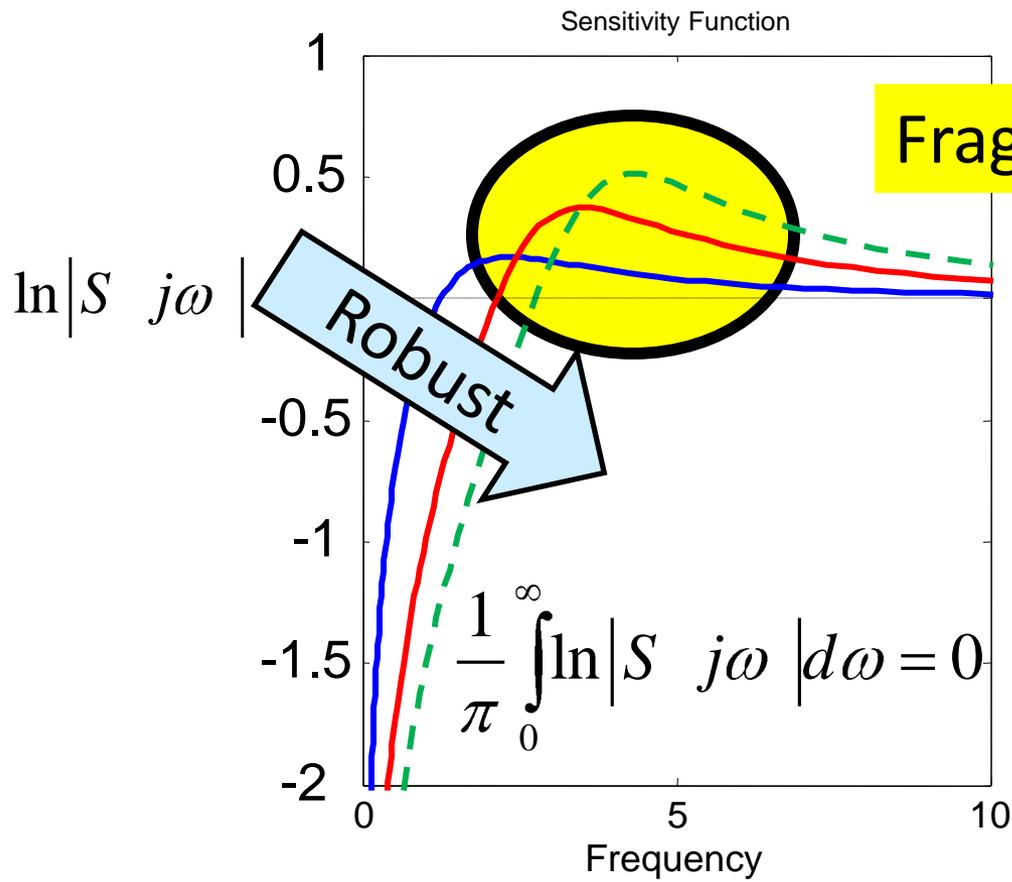
$$\ln|WS(j\omega)| = \ln|W(j\omega)| + \ln|S(j\omega)|$$

Gratuitous fragility versus fragile robustness

$$\int_0^{\infty} \ln |S(j\omega)| d\omega \geq 0$$

□ \Rightarrow Gratuitous fragility

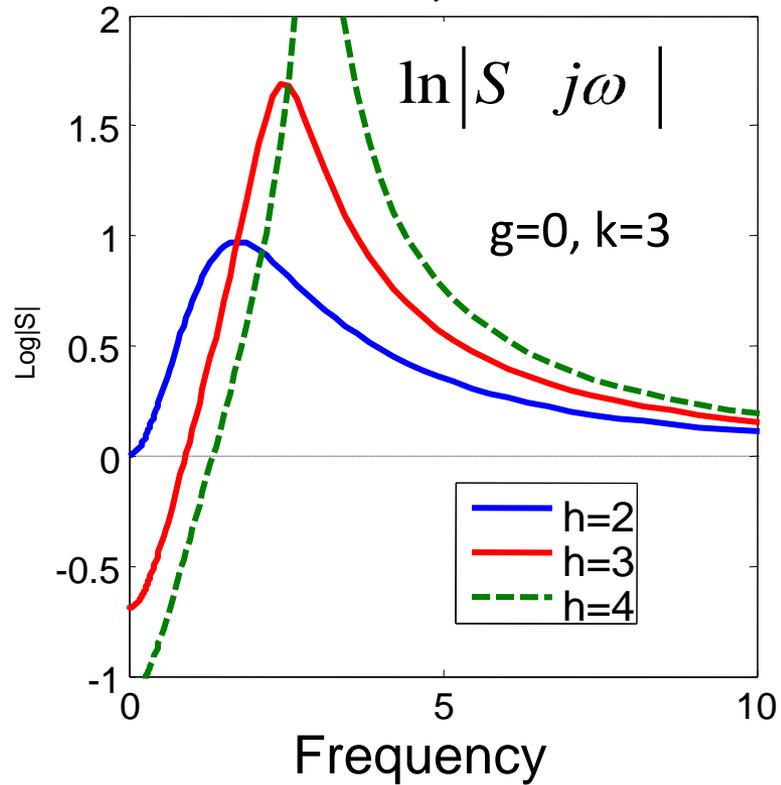
= \Rightarrow Fragile robustness



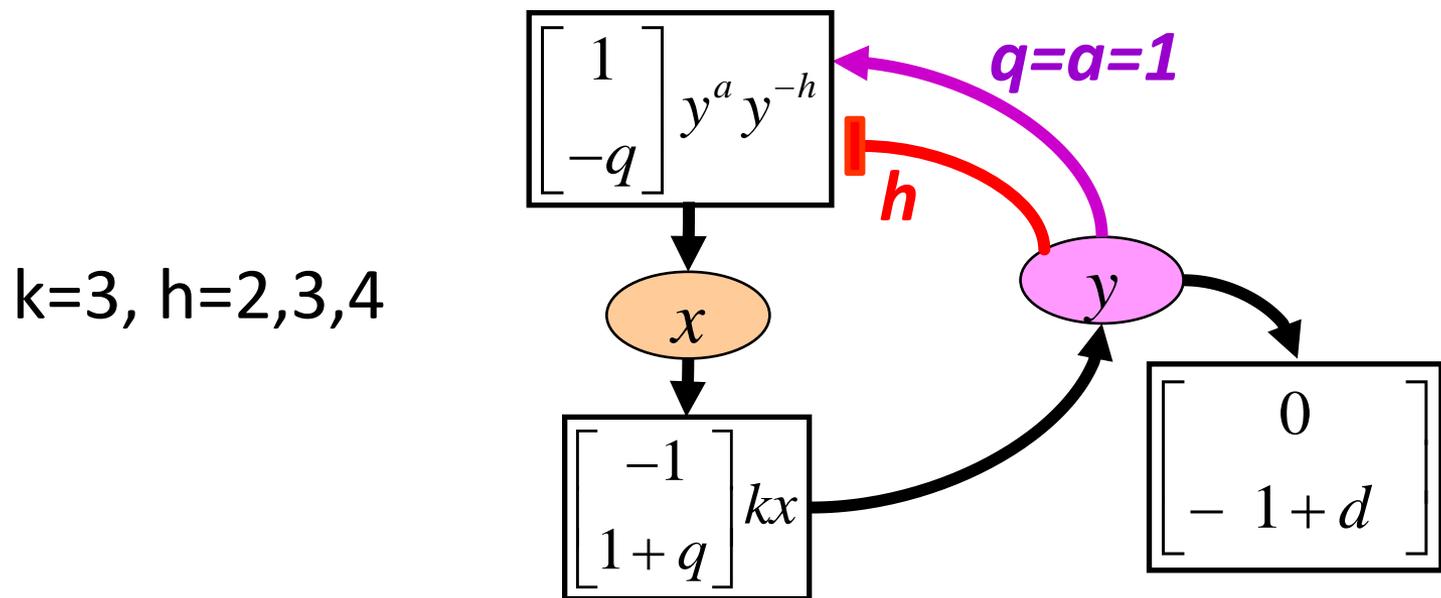
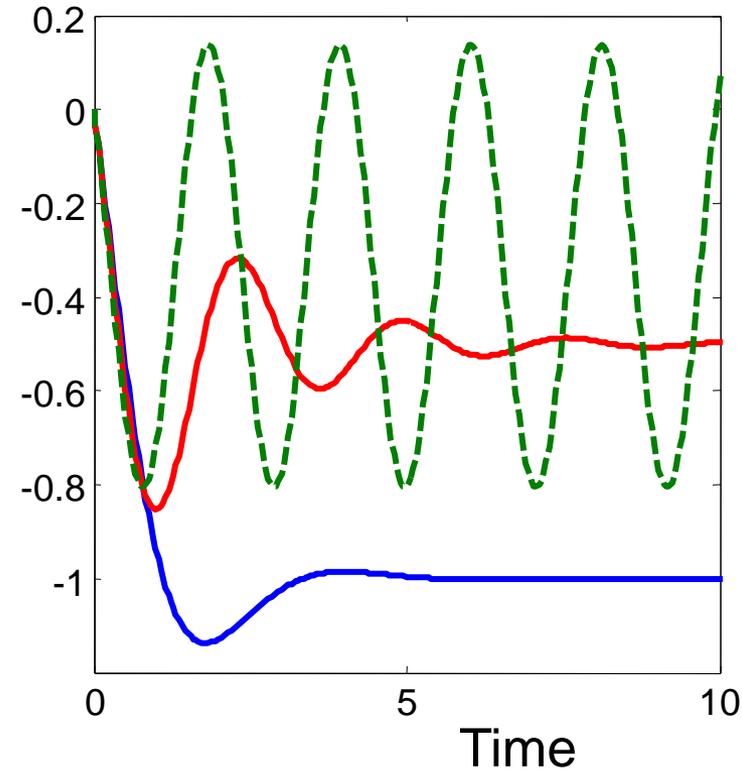
$$\text{Thm: } \frac{1}{\pi} \int_0^{\infty} \ln|S(j\omega)| d\omega \geq 0$$

$$\ln|WS(j\omega)| = \ln|W(j\omega)| + \ln|S(j\omega)|$$

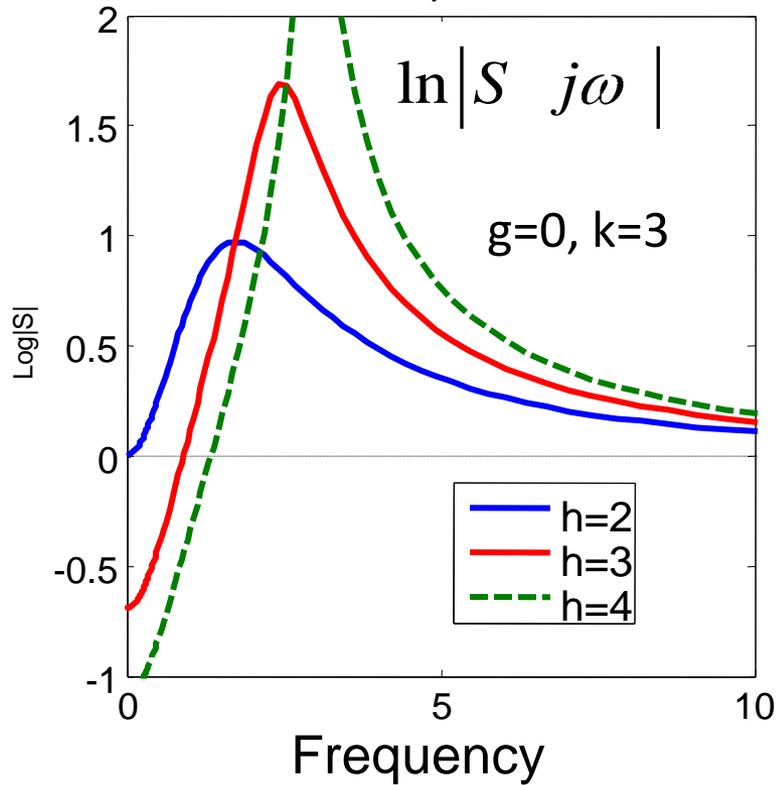
Sensitivity Function



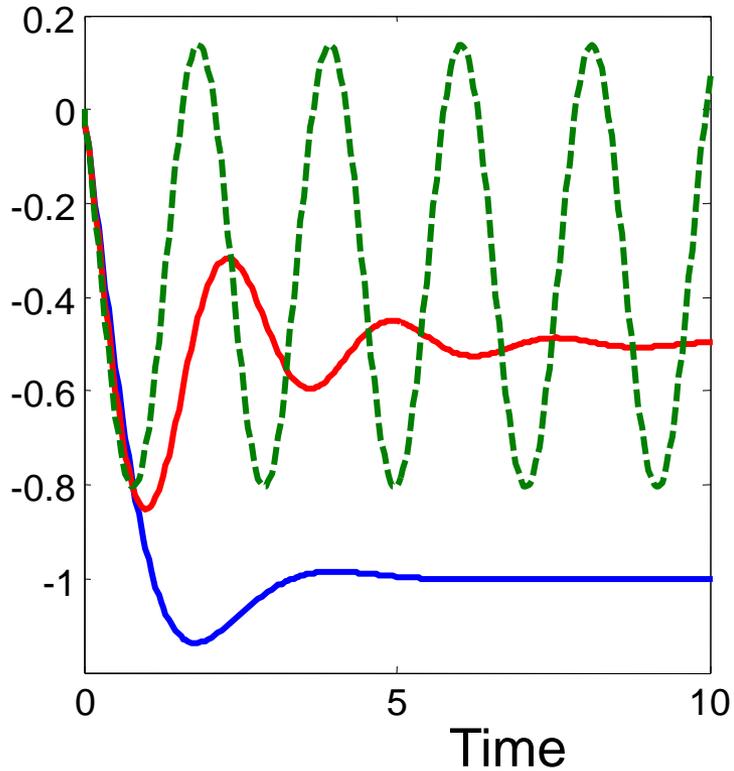
Time Simulation



Sensitivity Function



Time Simulation



$$\frac{1}{\pi} \int_0^{\infty} \ln|S(j\omega)| \left(\frac{z}{z^2 + \omega^2} \right) d\omega \geq \ln \left| \frac{z+p}{z-p} \right|$$

$$z = \frac{k}{q} \quad p = \text{RHP zero } s^2 + (k + g + q(a + g))s - ka$$

Small z is bad

	h	g	k	q	a
↑Complexity	↑	↑		↑	↑
↑Overhead	↑	↑	↑	↓	↓
↑Enzyme size	↑	↑	↑		
↑Enzyme #			↑		
Autocatalysis				↓	↓

↑Fragile/dist.	↓				↑
↑Fragile/oscill.	↑	↓	↓	↑	

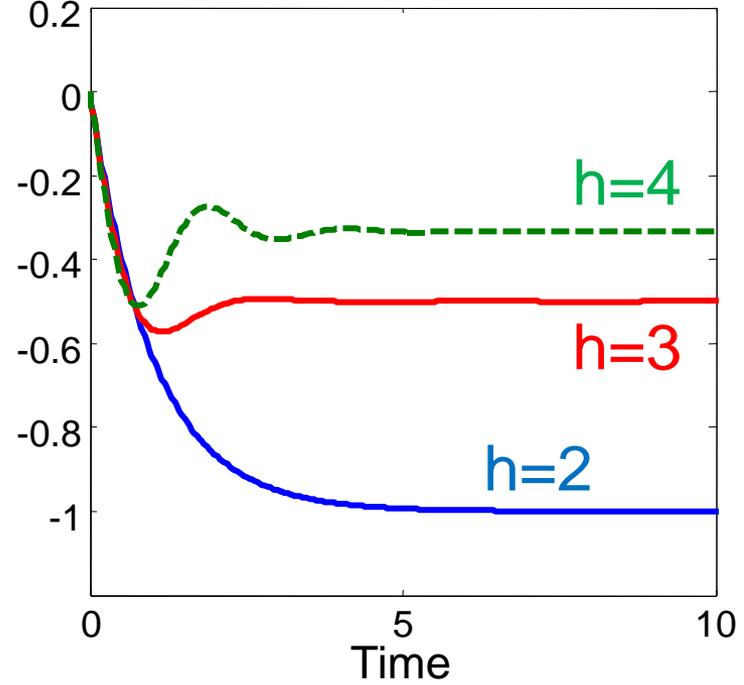
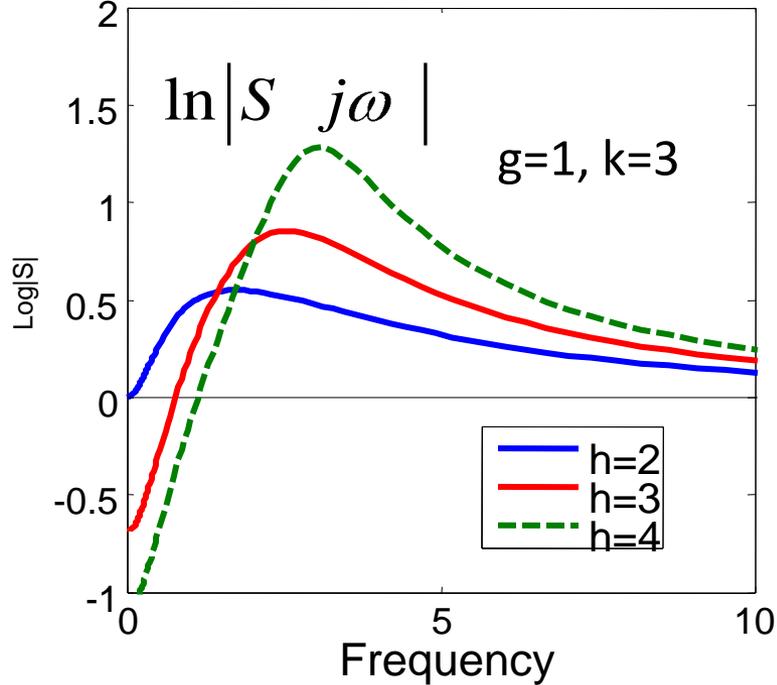
$$z = \frac{k}{q}$$

Large k good
Large q bad

$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| \left(\frac{z}{z^2 + \omega^2} \right) d\omega \geq \ln \left| \frac{z+p}{z-p} \right|$$

$$z = \frac{k}{q} \quad p = \text{RHP zero } s^2 + (k + g + q(a + g))s - ka$$

Small z is bad

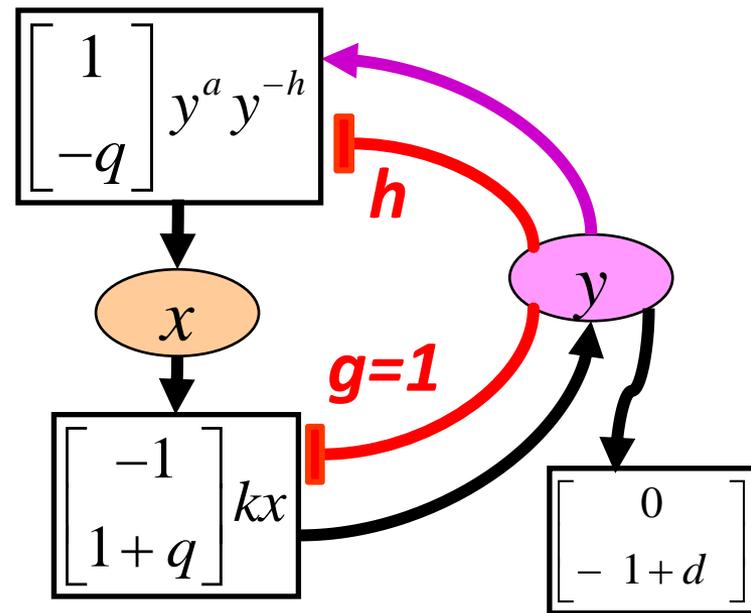


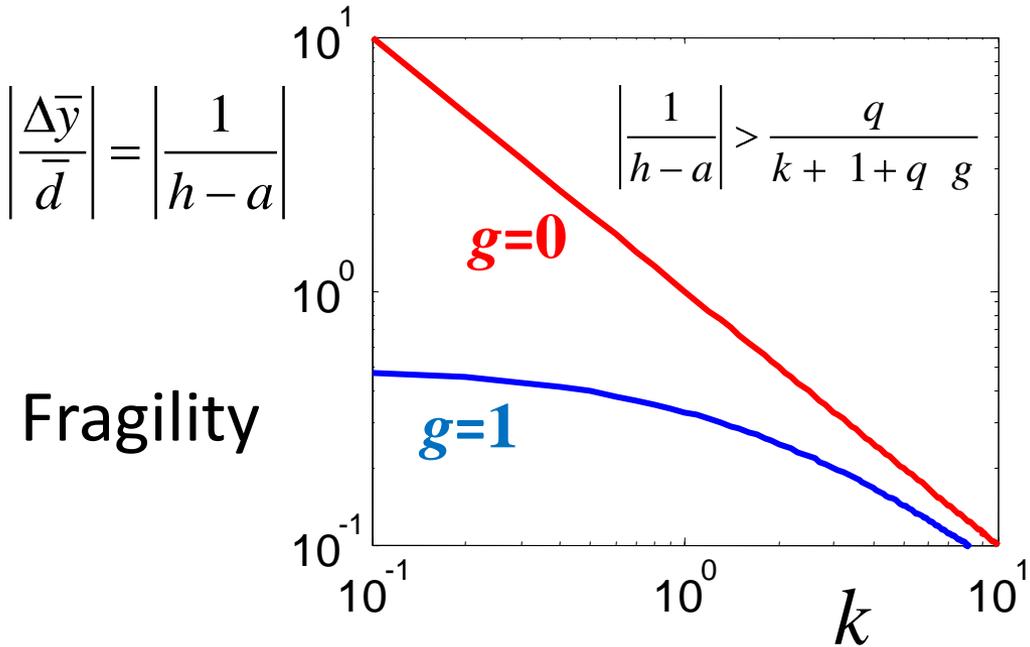
$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| \left(\frac{z}{z^2 + \omega^2} \right) d\omega \geq \ln \left| \frac{z+p}{z-p} \right|$$

$$z = \frac{k}{q} \quad \text{Small } z \text{ is bad}$$

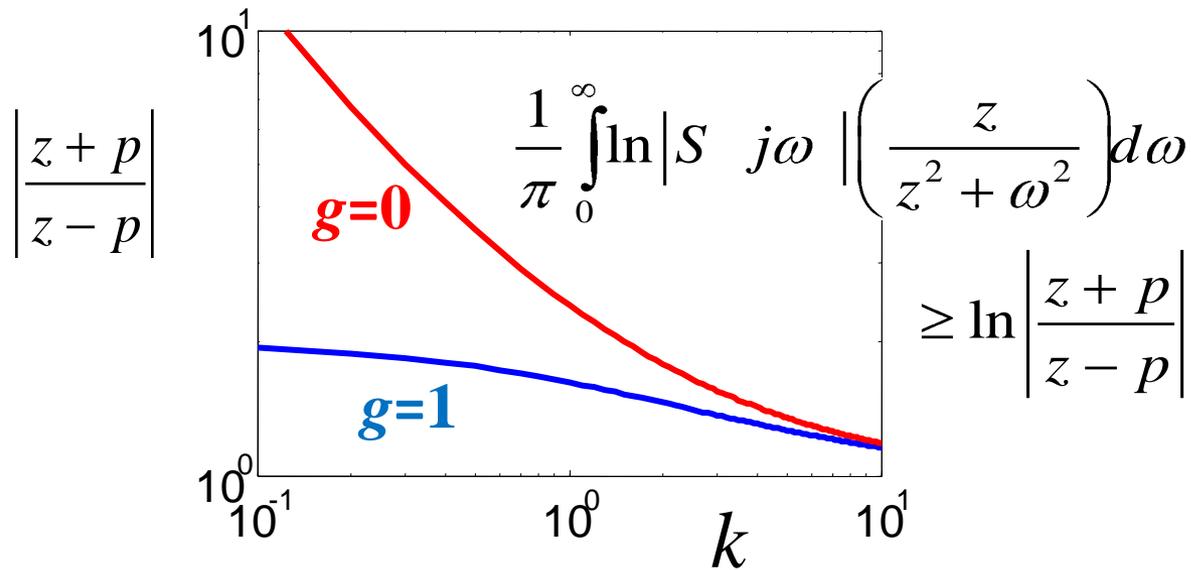
$$p = \text{RHP zero } s^2 + (k + g + q(a + g))s - ka$$

Small p is good



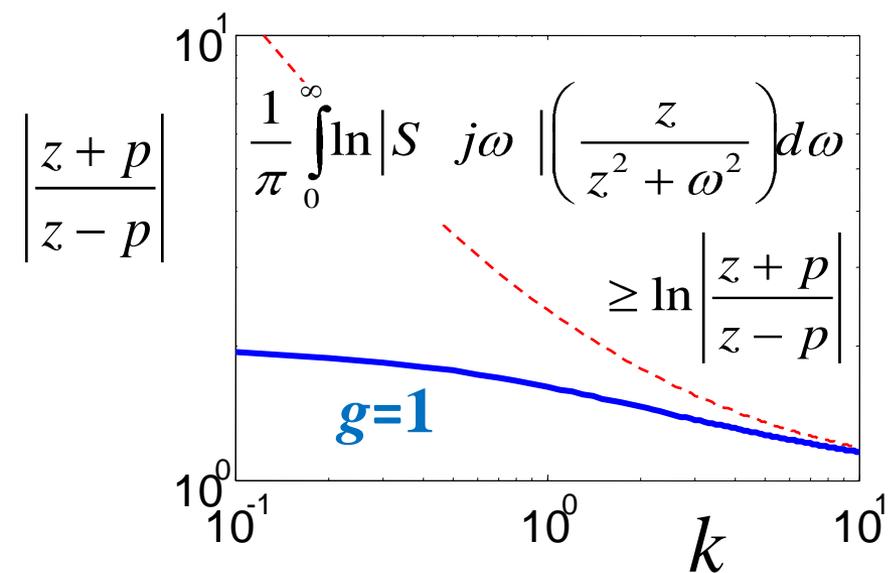
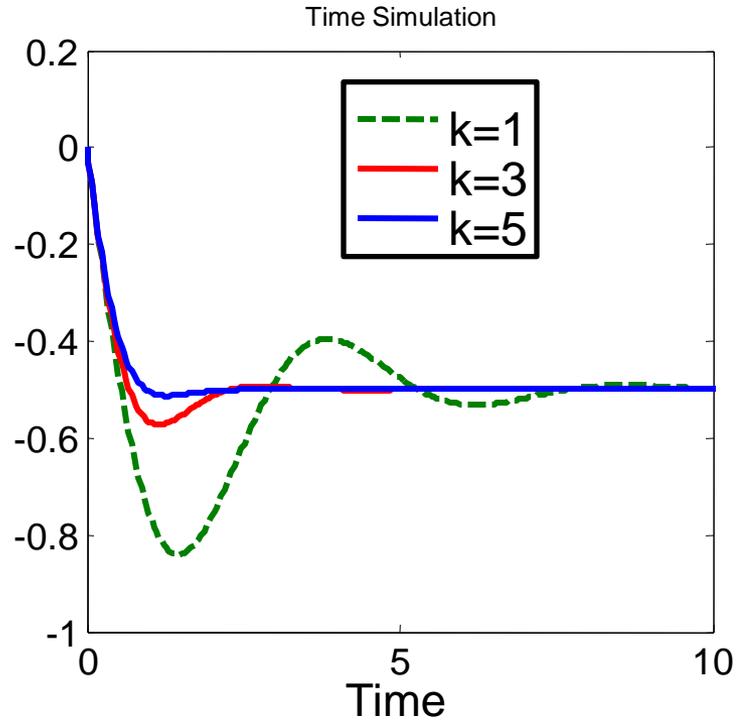
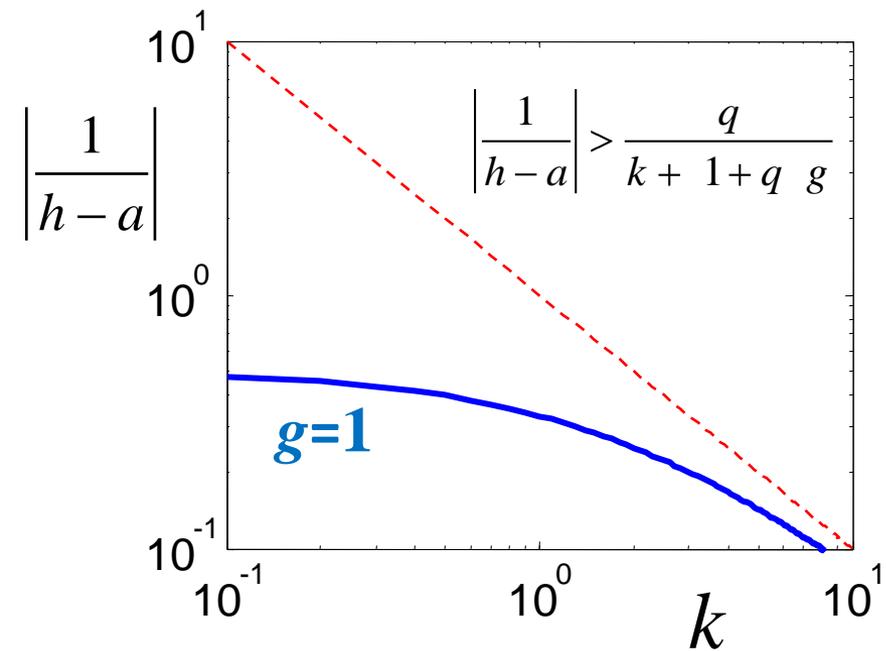


Static + stability +
phenomenology

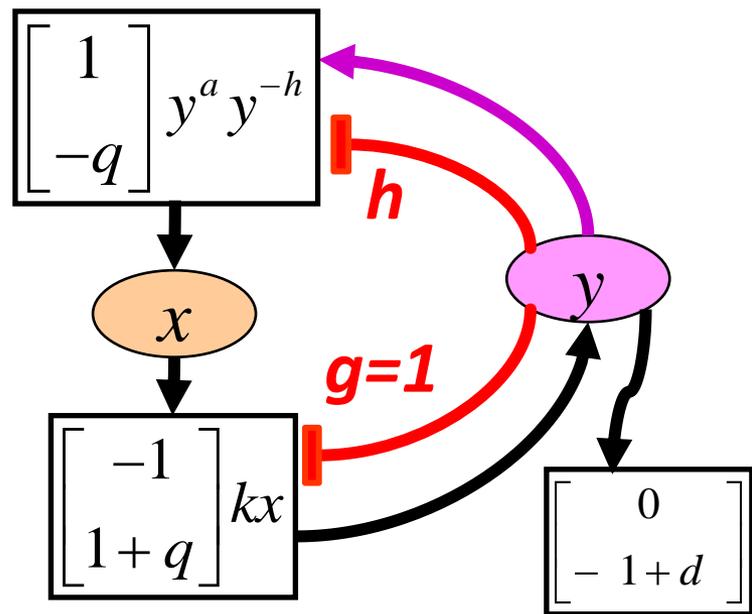


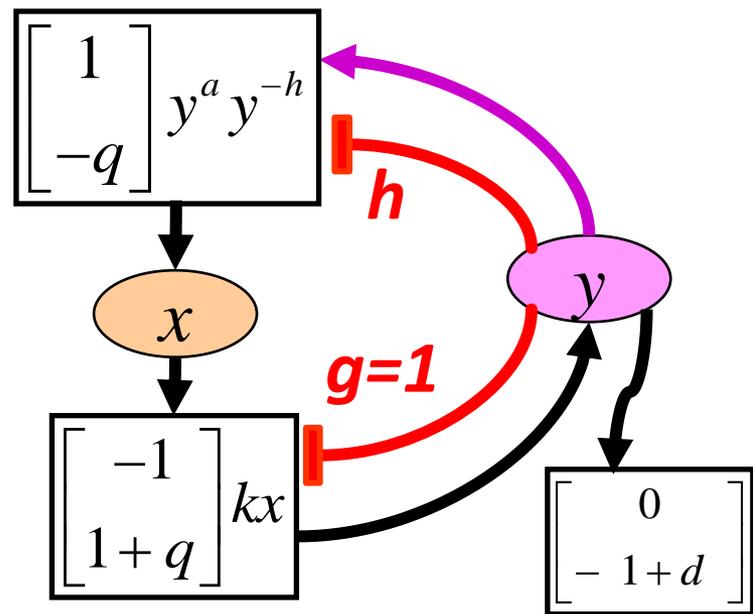
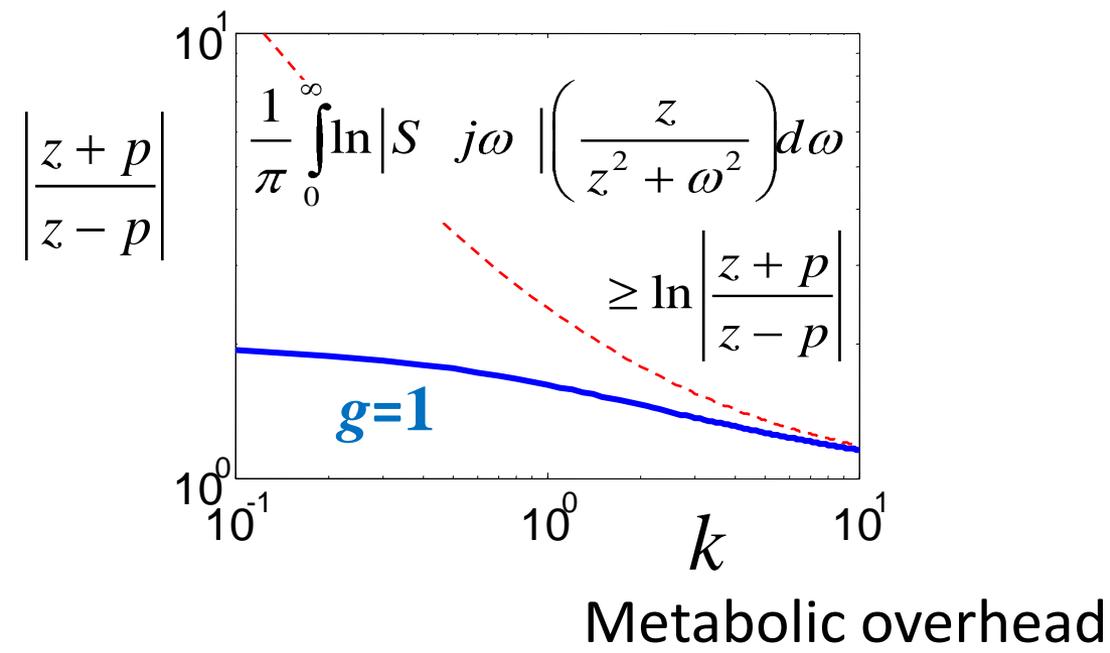
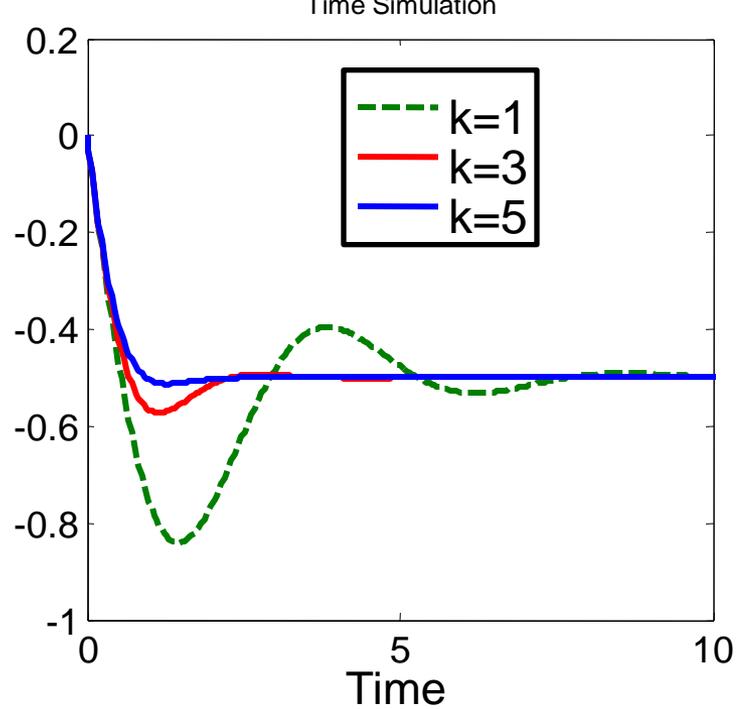
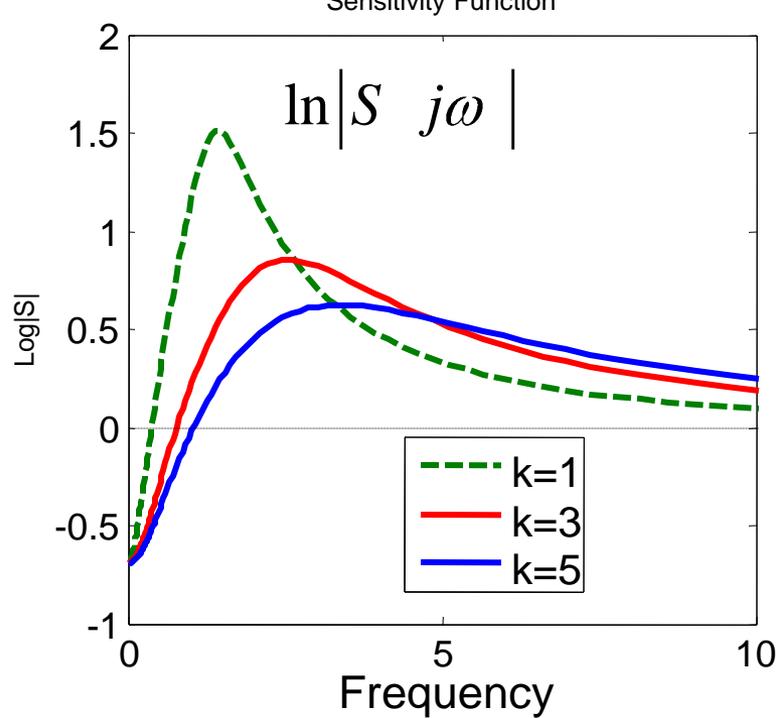
Metabolic overhead

Dynamic
+ rigor



Metabolic overhead



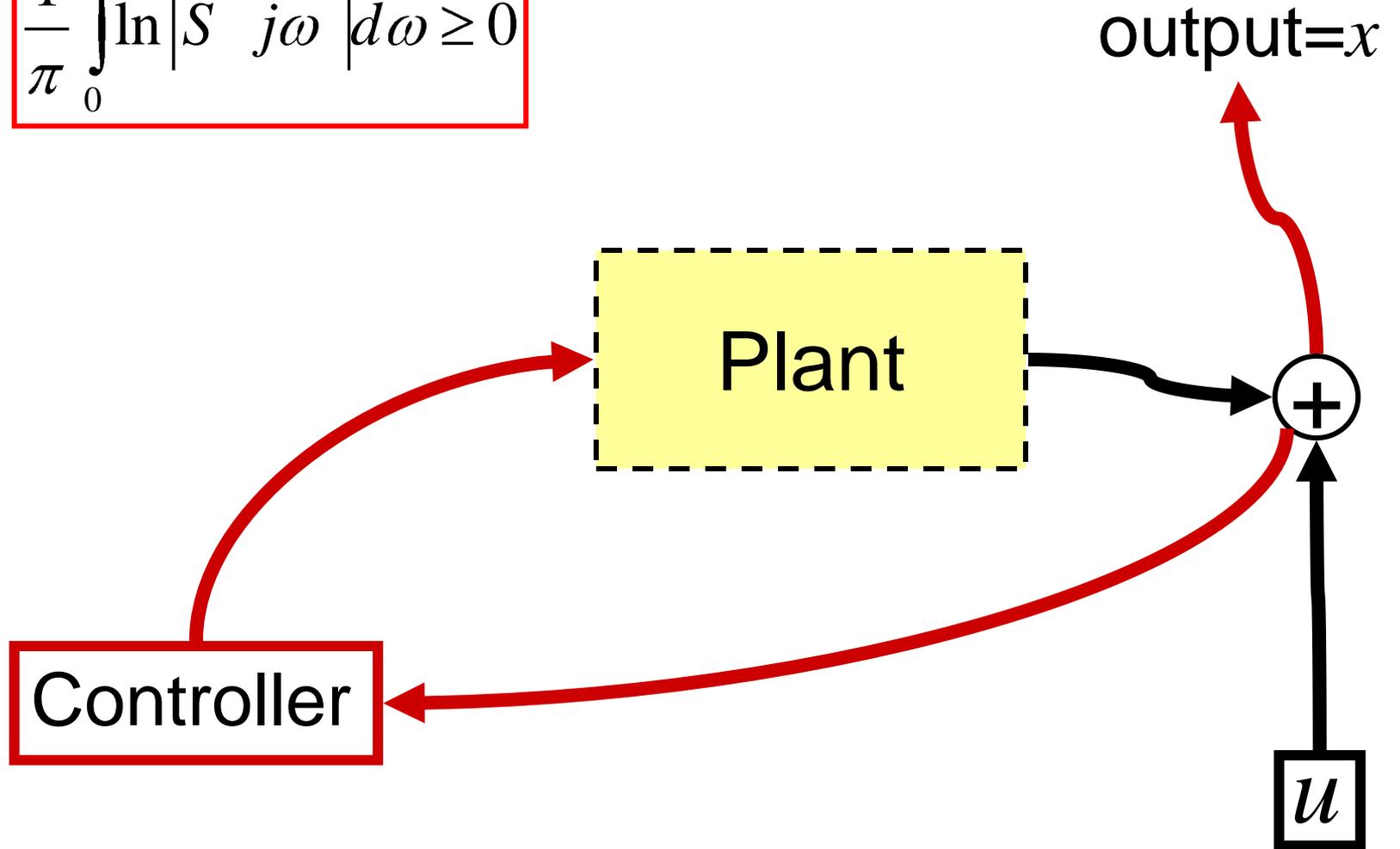


$$\frac{1}{\pi} \int_0^{\infty} \ln \left| S(j\omega) \right| \frac{z}{z^2 + \omega^2} d\omega \geq \ln \left| \frac{z+p}{z-p} \right|$$

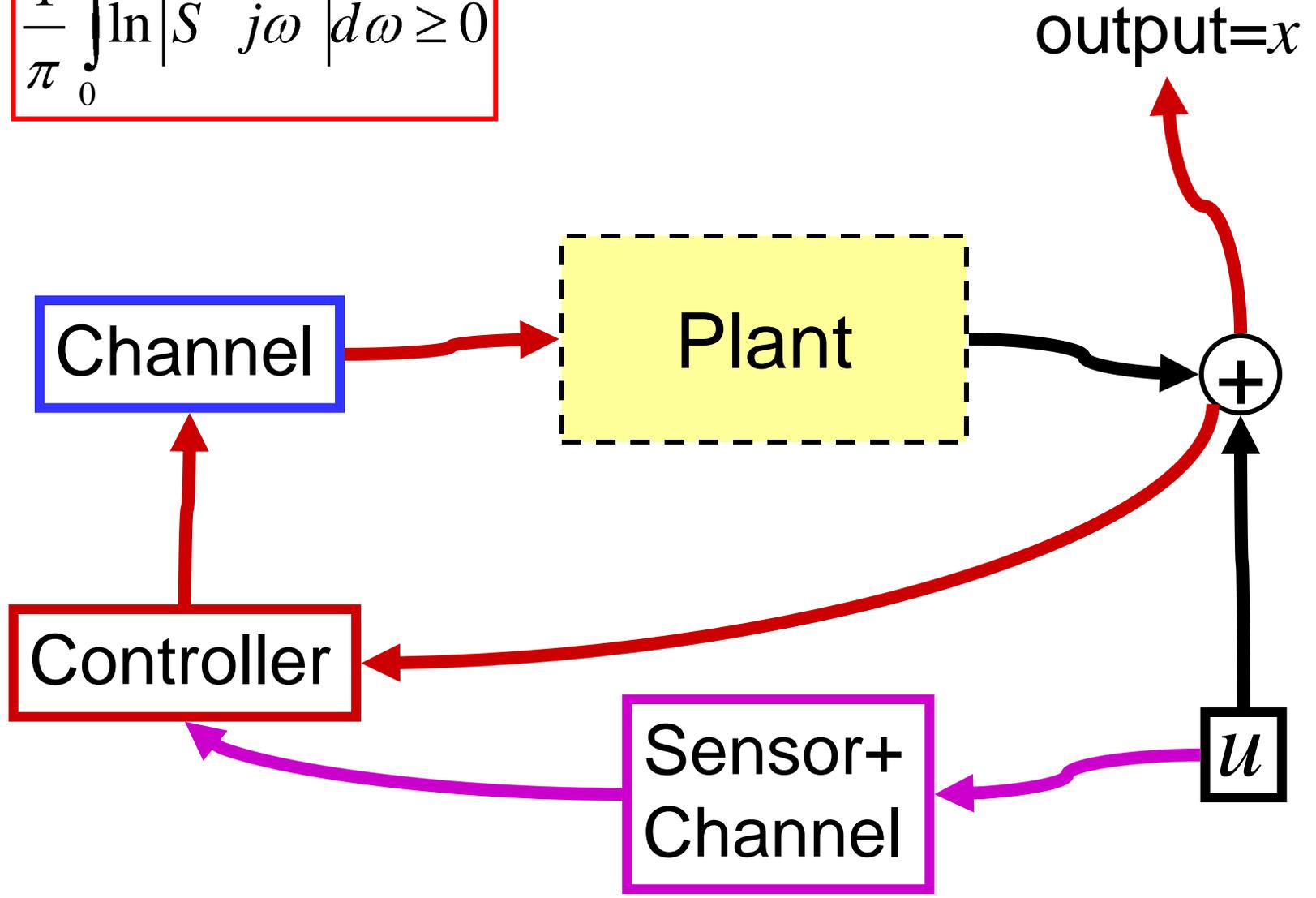
Robustness tradeoffs aggravated by

- Autocatalytic feedback (essential for life)
- Efficient processes
 - Minimal enzymes (lean manufacturing)
 - Long assembly process (simple steps)
- Limited control feedback

$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| d\omega \geq 0$$



$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| d\omega \geq 0$$

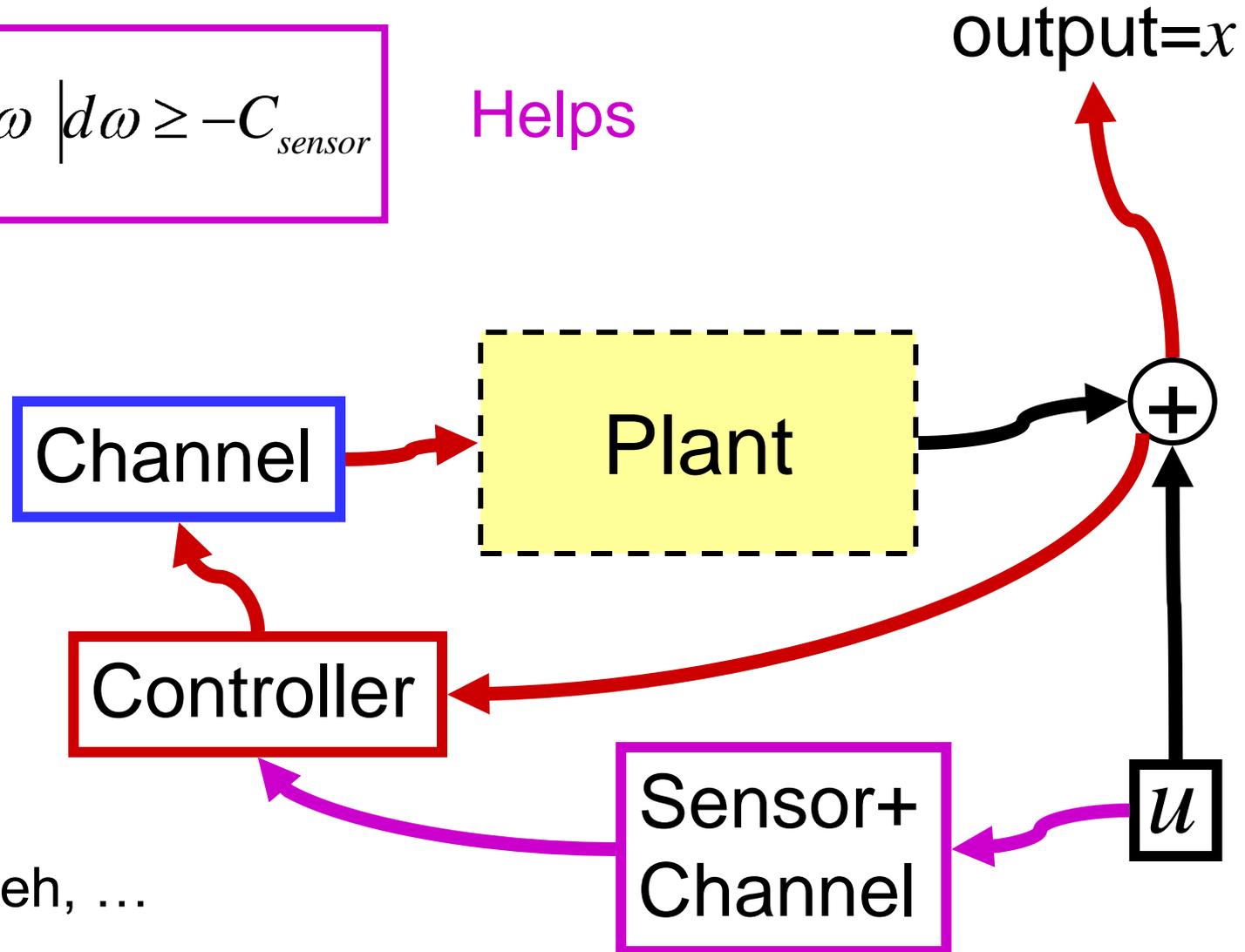


$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| d\omega \geq -C_{FB}$$

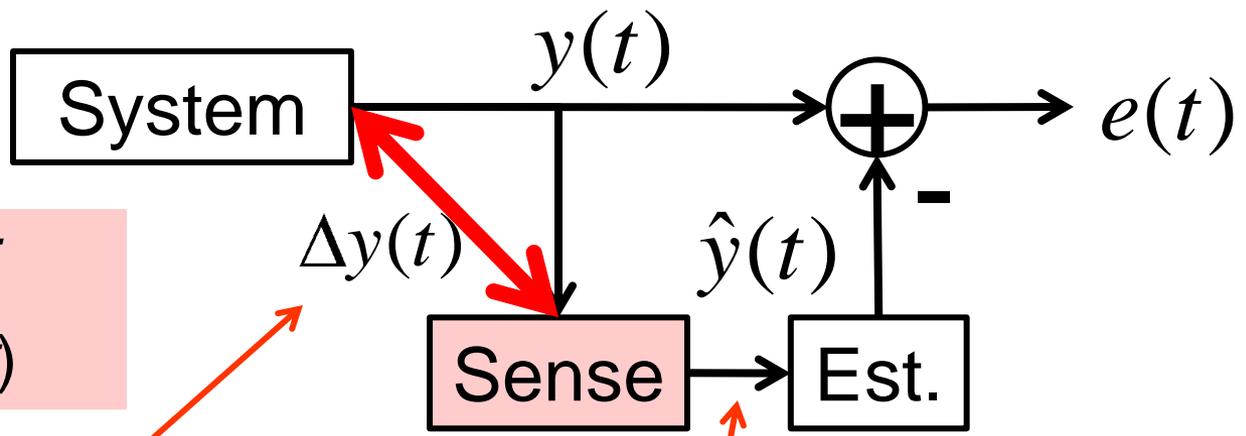
Hurts

$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| d\omega \geq -C_{sensor}$$

Helps



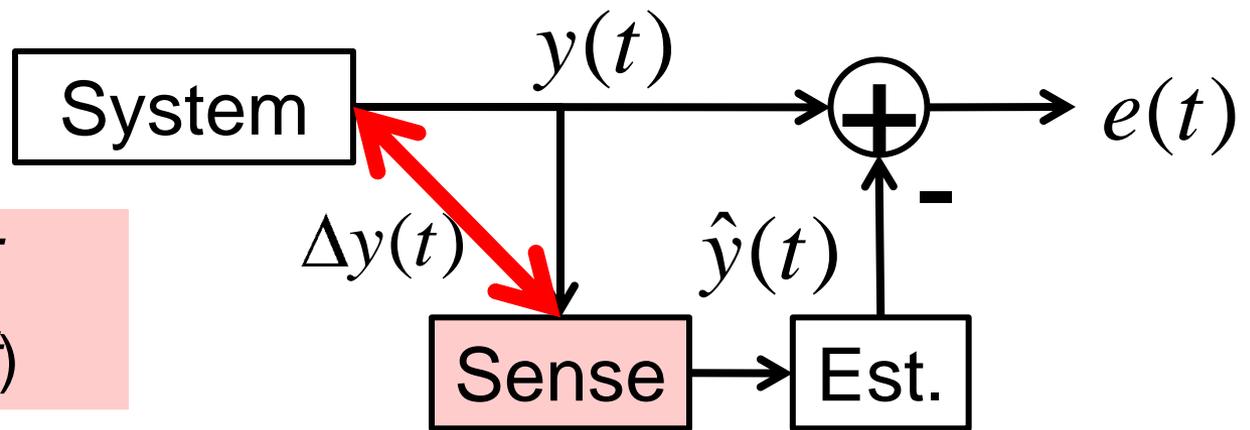
- Sensor at temp T
- Short interval $(0, t)$



Back action

Sensor “noise”

Assume “physical” sensor



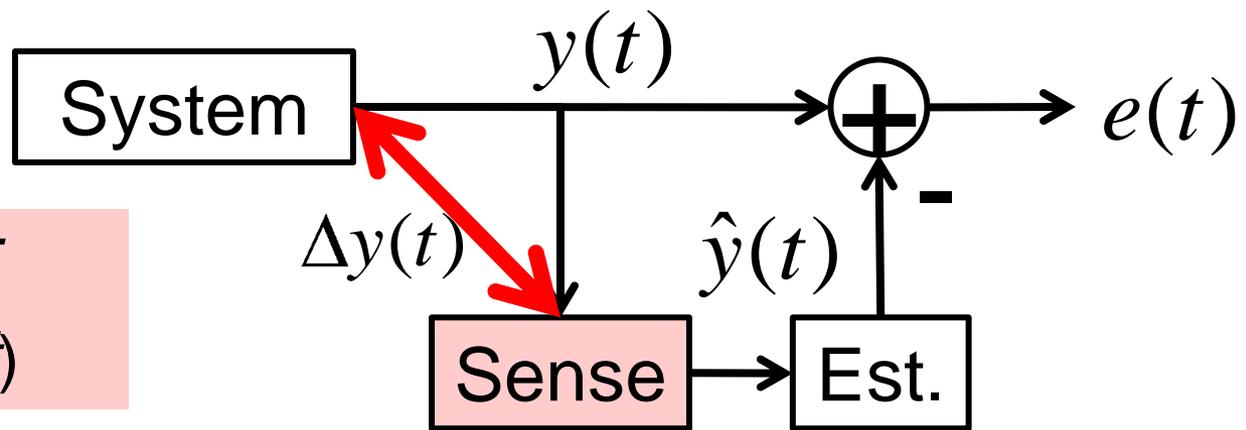
- Sensor at temp T
- Short interval $(0, t)$

Back action

$$E \Delta y^2(t) \geq kTt + O(t^2)$$

Sensor "noise"

$$E e^2(t) \geq \frac{kT}{t} + O(1)$$



- Sensor at temp T
- Short interval $(0, t)$

$$E \Delta y^2(t) \geq kTt + O t^2$$

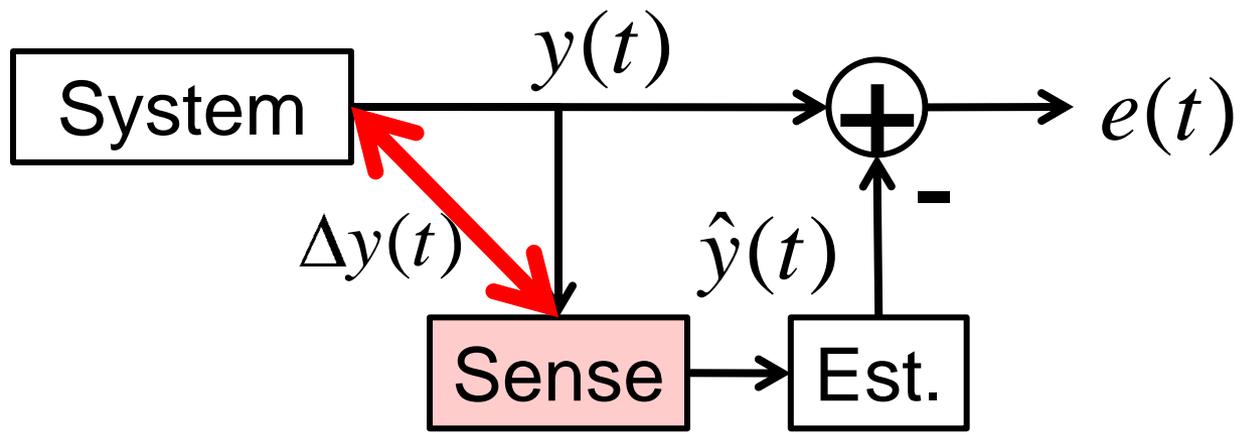
Back action

$$E e^2(t) \geq \frac{kT}{t} + O 1$$

Sensor "noise"

- Simplest hard tradeoffs on speed and errors
- More tradeoffs (energy overhead vs speed vs errors)
- Just scratching the surface
- Actuators, computation, quantum effects, ...?
- Aside: linear active elements need nonlinear implementation

$|\Delta y(t)|$ Back action



A transient and far-from-equilibrium upgrade of statistical mechanics

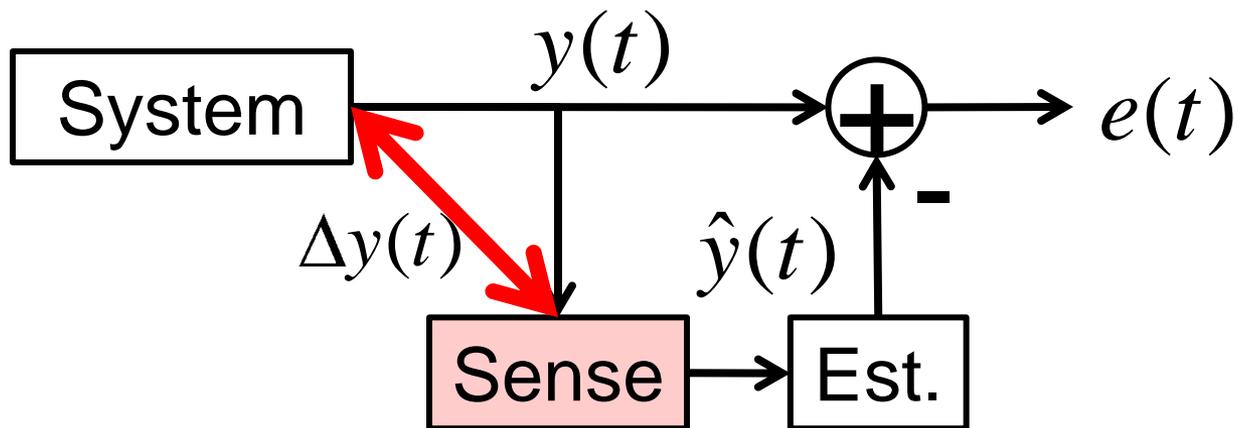
$E \Delta y^2(t) \geq kTt$

$E e^2(t) \geq \frac{kT}{t}$

Estimation error

$|e(t)|$





A transient and far-from-equilibrium upgrade of statistical mechanics

$$|\Delta y(t)| |e(t)| \geq kT + O(t)$$

$$E e^2(t) \geq \frac{kT}{t}$$

$$E \Delta y^2(t) \geq kTt$$

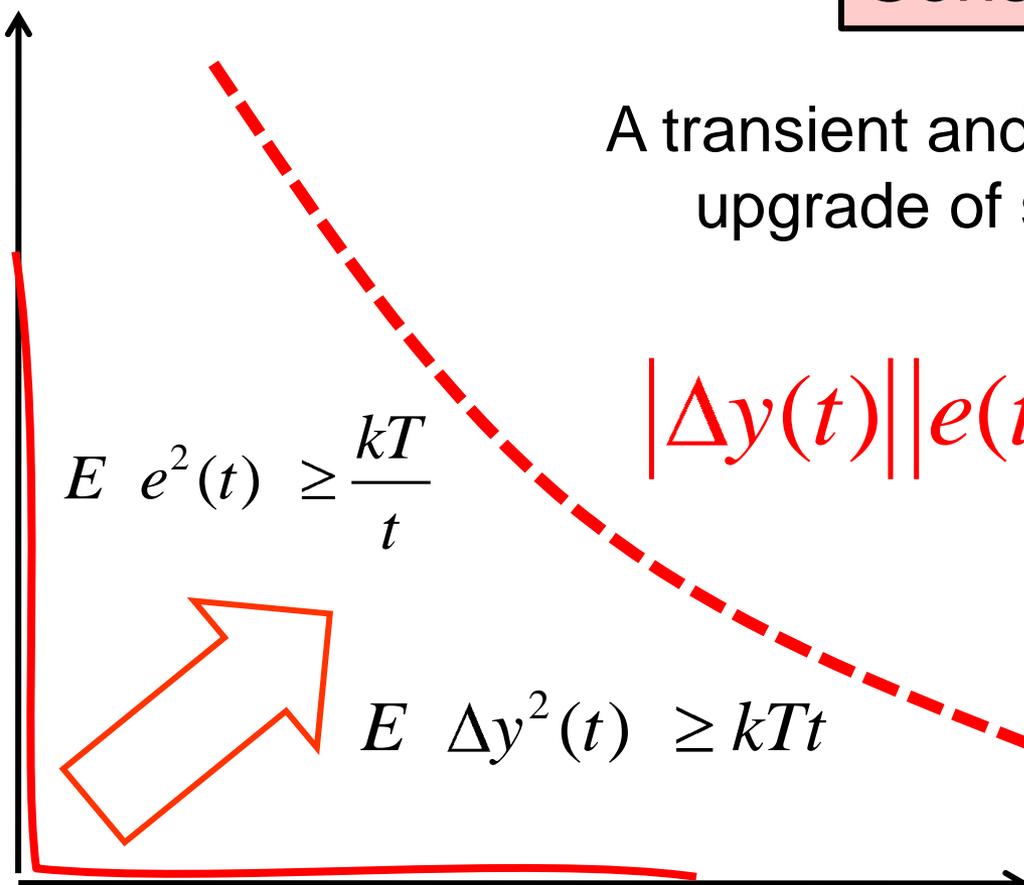
Cold sensors are better and faster (but not cheaper)

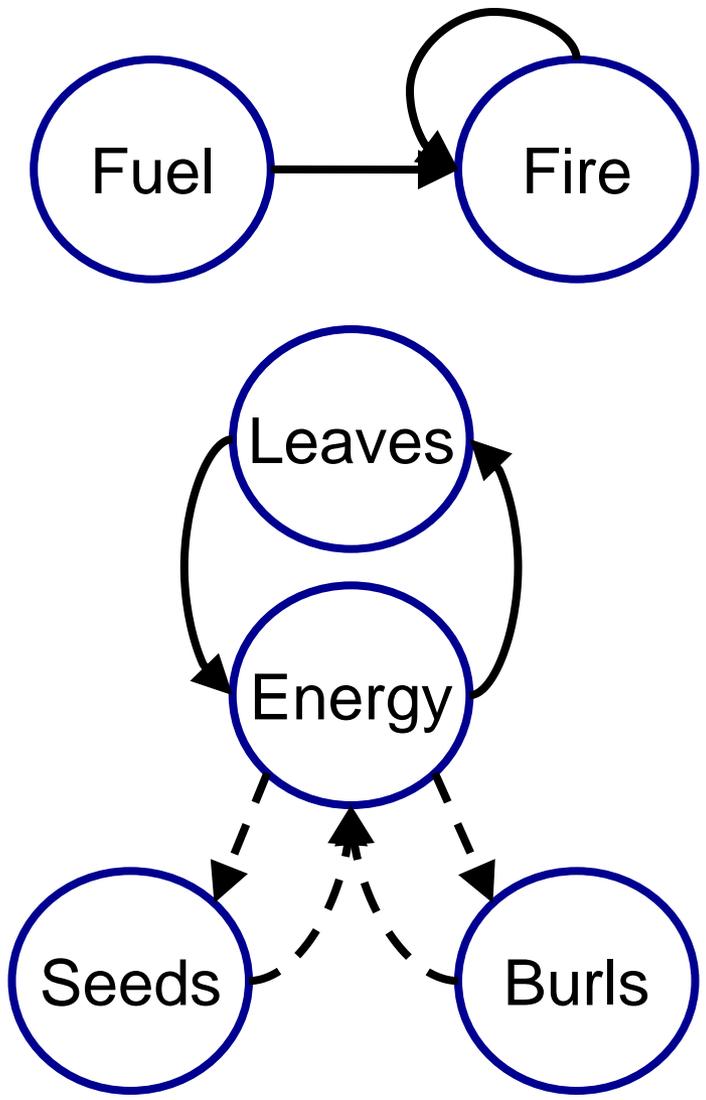
Error

$|e(t)|$

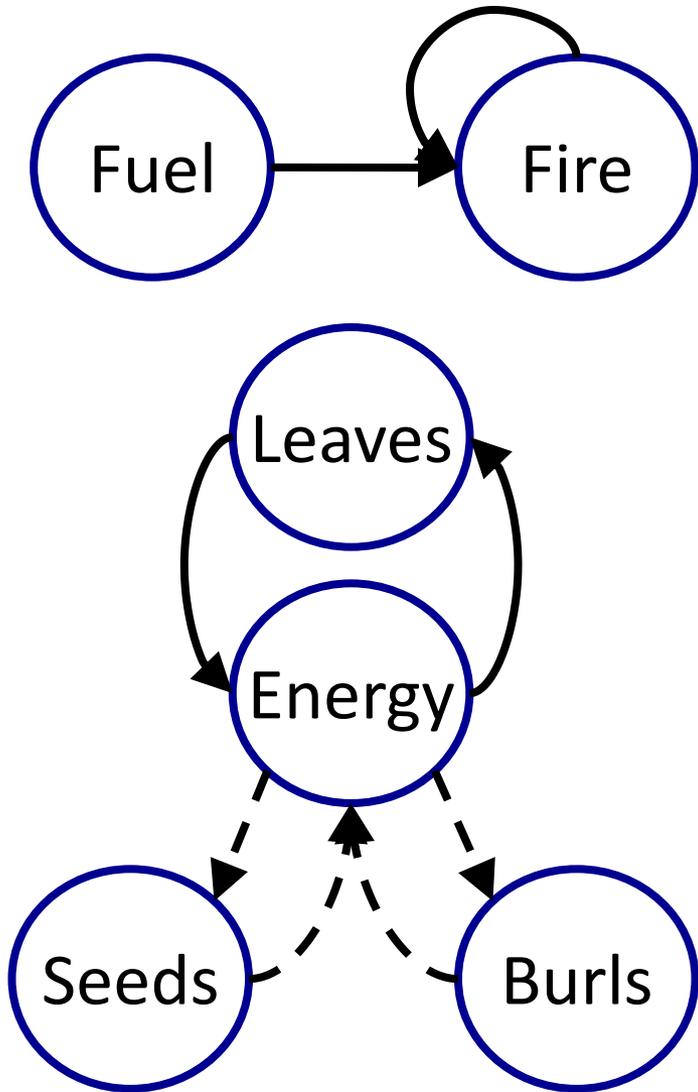
Back action

$|\Delta y(t)|$





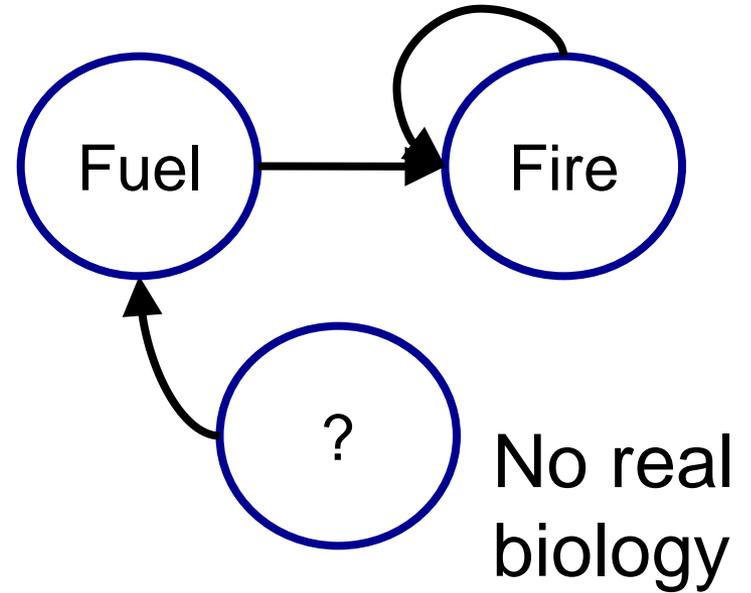
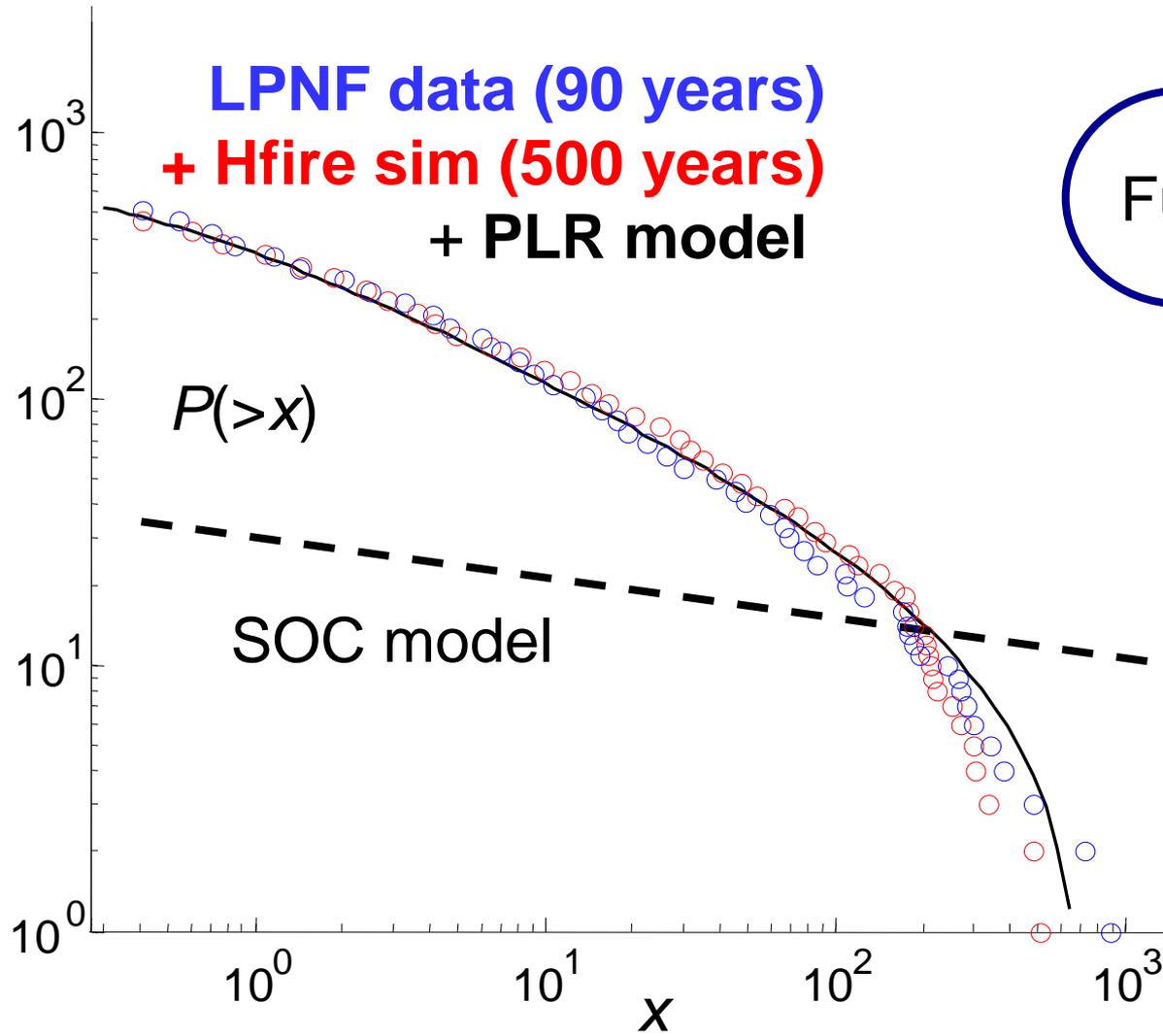
Fire ecology
as
metabolism?



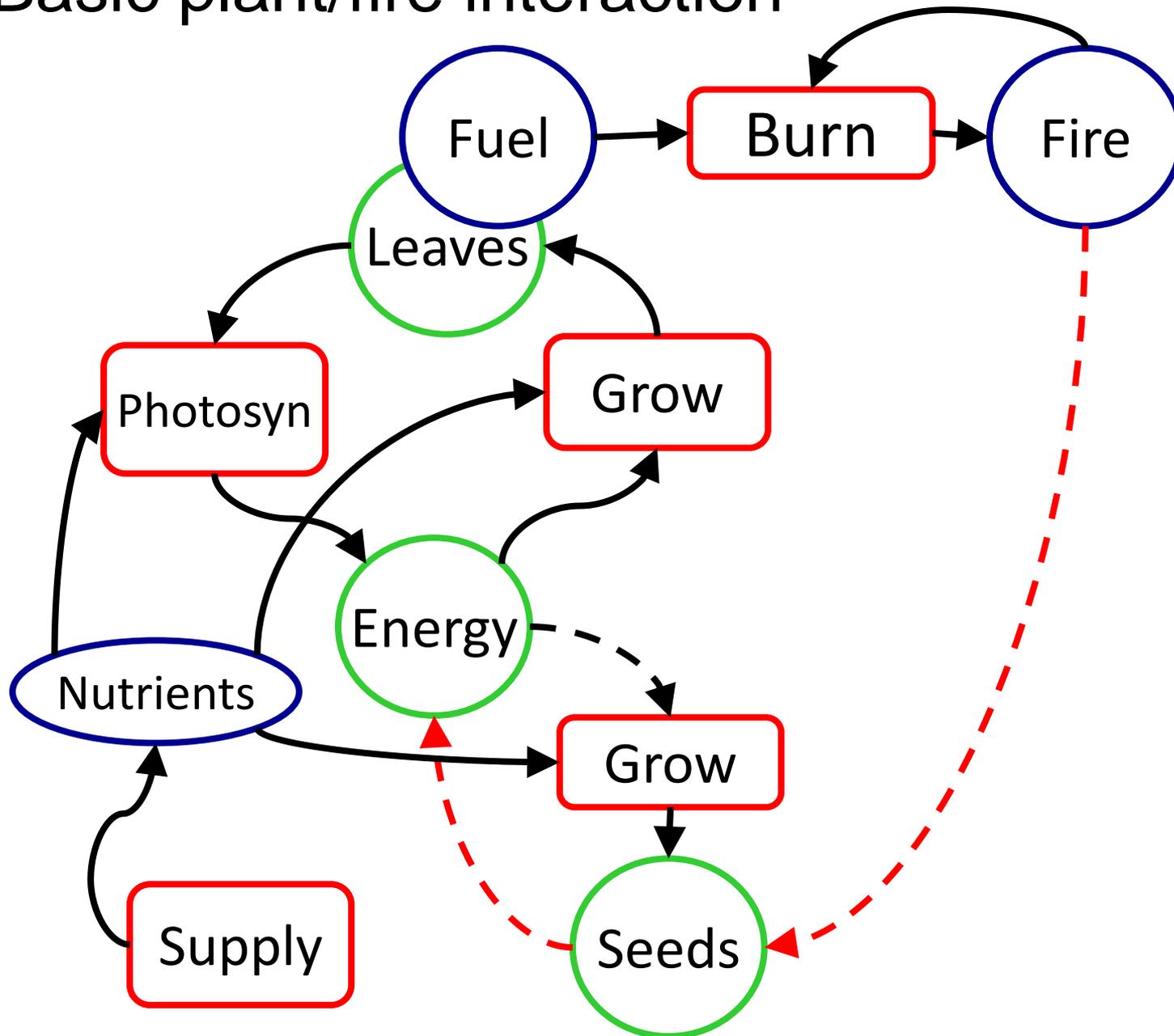
Scientific toolbox

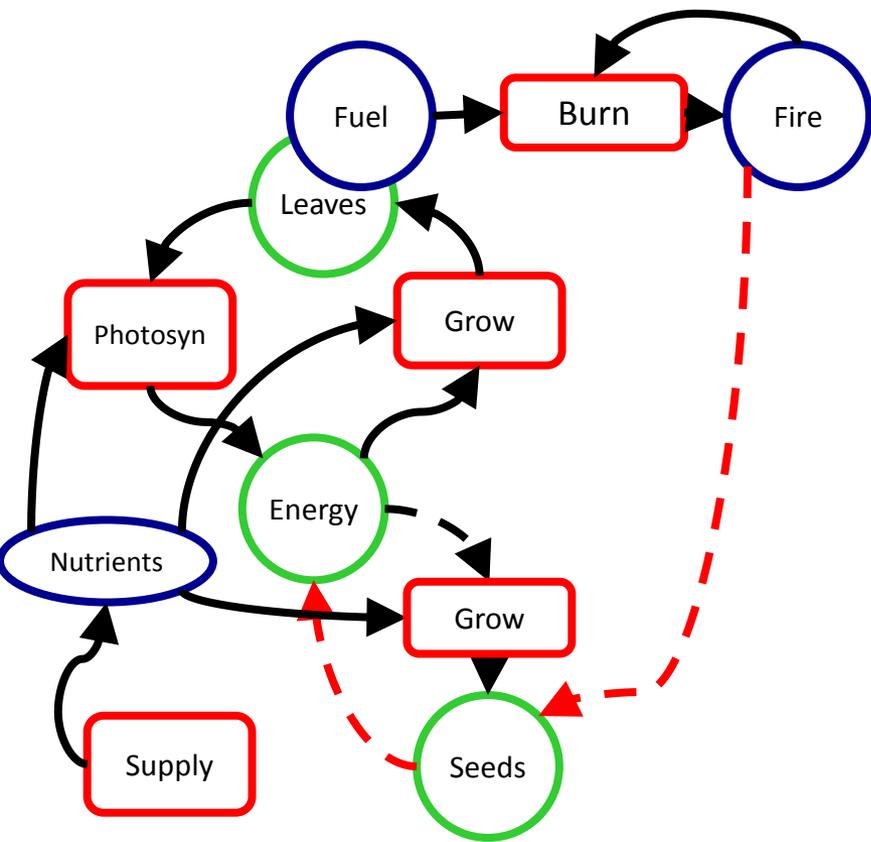
- Conservation laws/
constraints
 - Matter and energy
 - **Robustness/fragility**
- Feedback/Dynamics
 - Autocatalysis
 - Control

“Toy” models
(phenomenological)



Basic plant/fire interaction





Two strategies

Grass

- Annual
- Die or burn each year
- Grow leaves fast
- Small stored energy
- Shade intolerant
- Expands with frequent fire

Tree (forest type)

- Perennial, dies only if burned or old age
- Slow growth (leaves plus support)
- Larger stored energy
- Causes shade which kills grass
- Expands with infrequent fire

Universals in complex robust networks

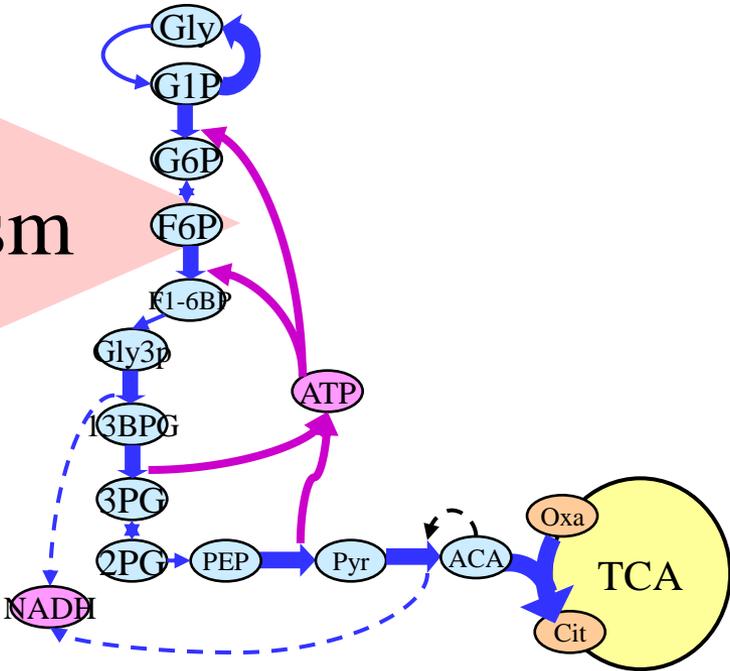
So far

- Behaviors
- Laws (constraints, tradeoffs)

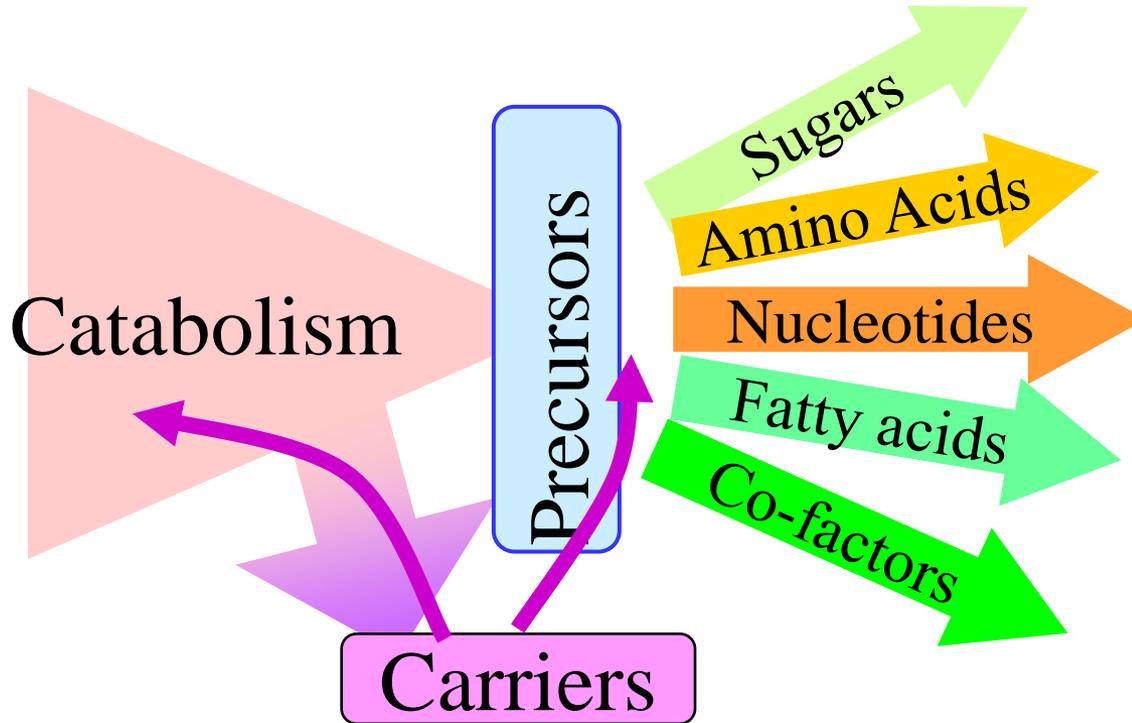
Next

- Architectures

Catabolism

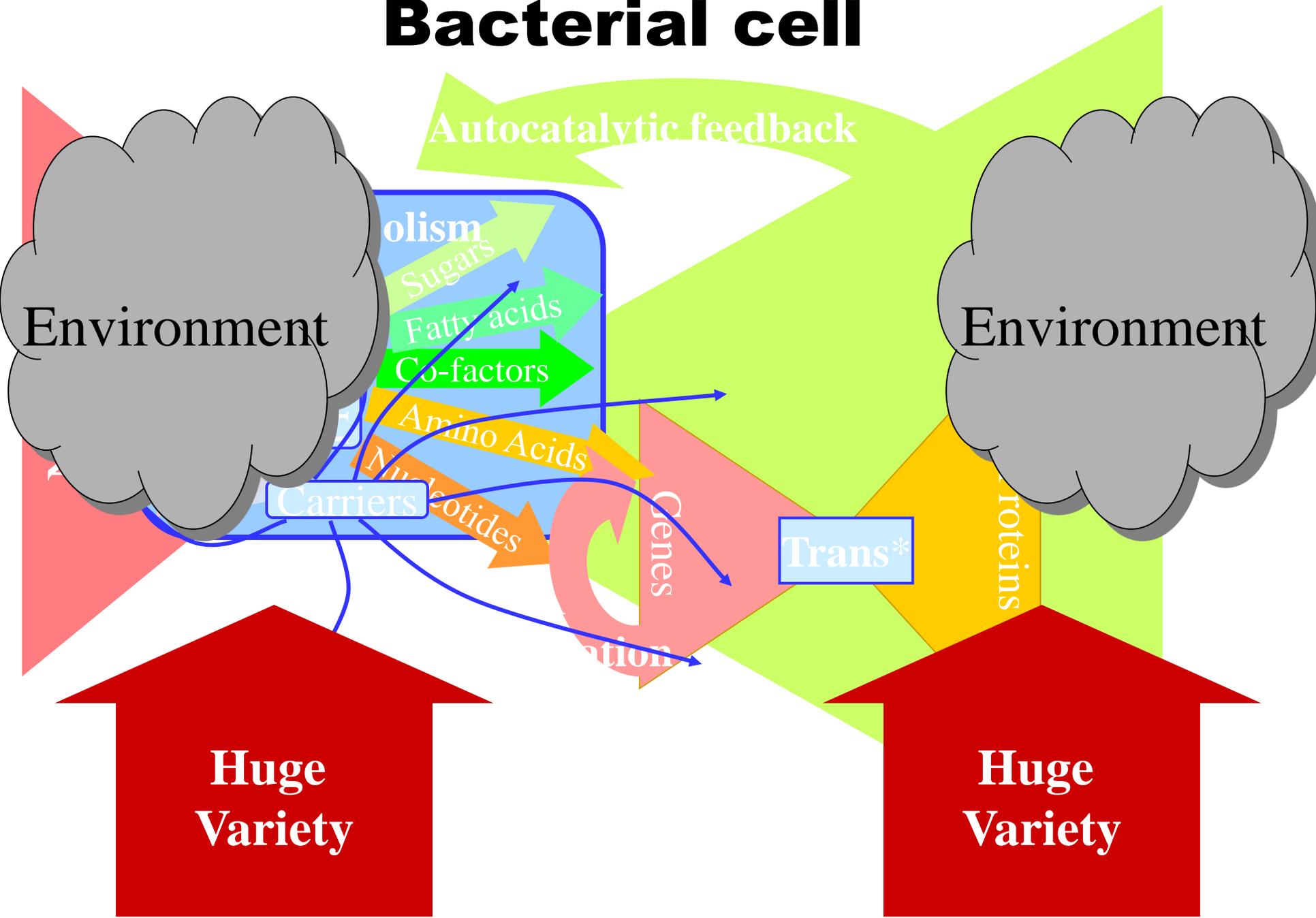


Inside every cell



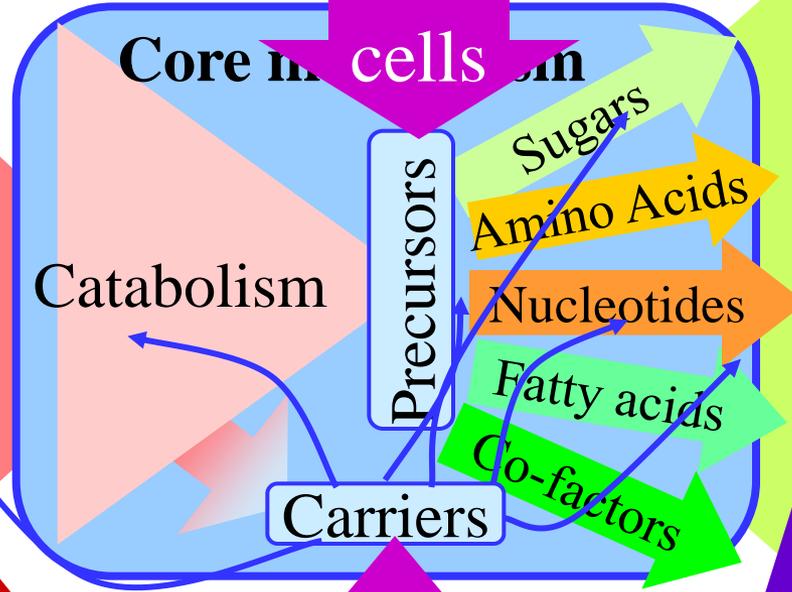
Core metabolic bowtie

Bacterial cell



Taxis and transport

Nutrients



**Same
12
in all
cells**

**Same
8
in all
cells**

**≈100
≈same
in all
organisms**

**Huge
Variety**

Taxis and transport

Autocatalytic feedback

Polymerization and complex assembly

Nutrients



Carriers

Genes

Trans*

Protein

Reproduction

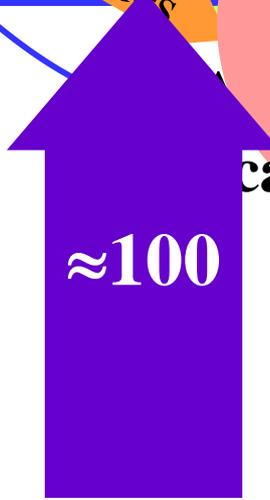
12

∞

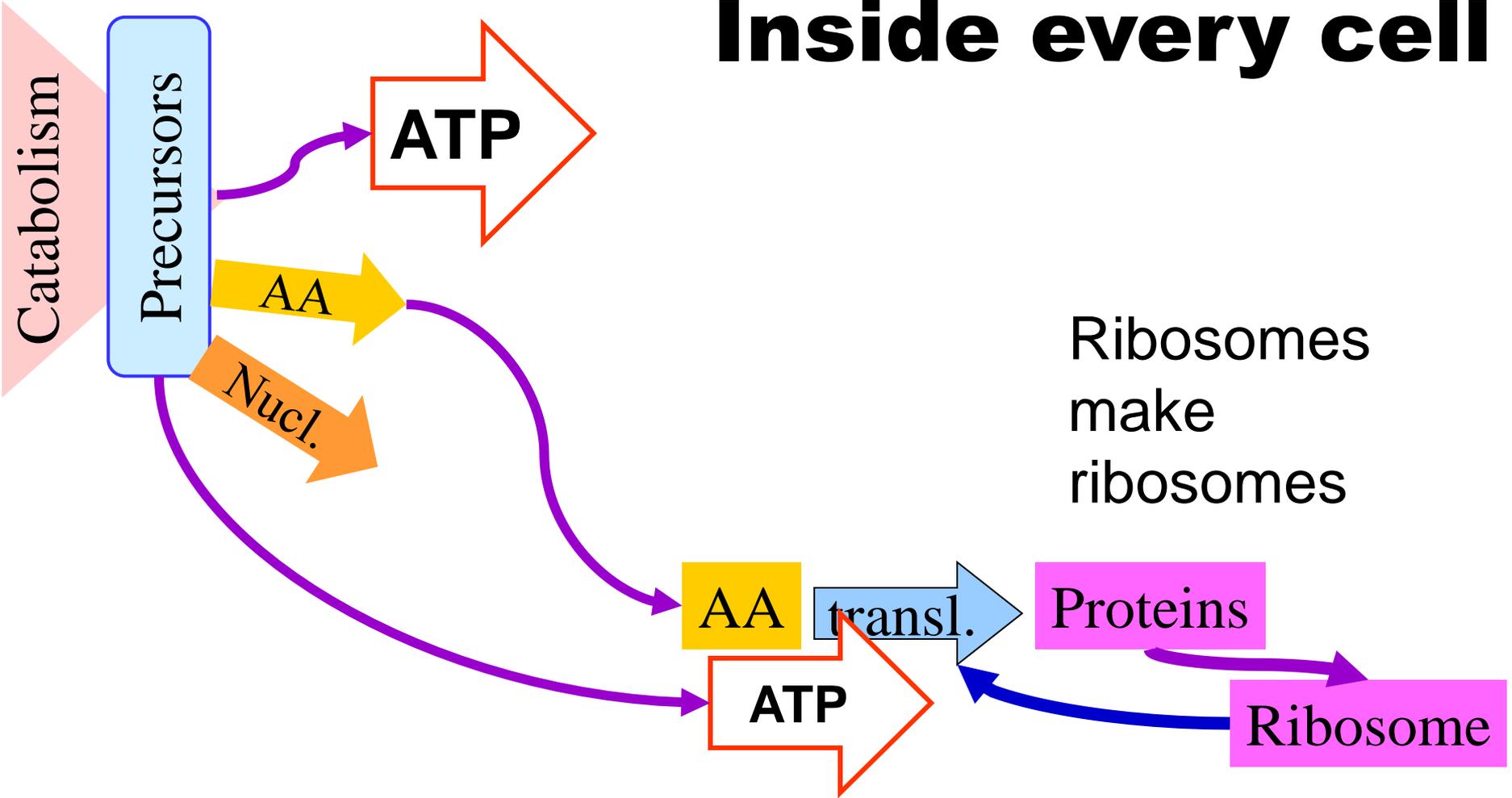
≈100

≈10⁴ to ≈ ∞
in one organisms

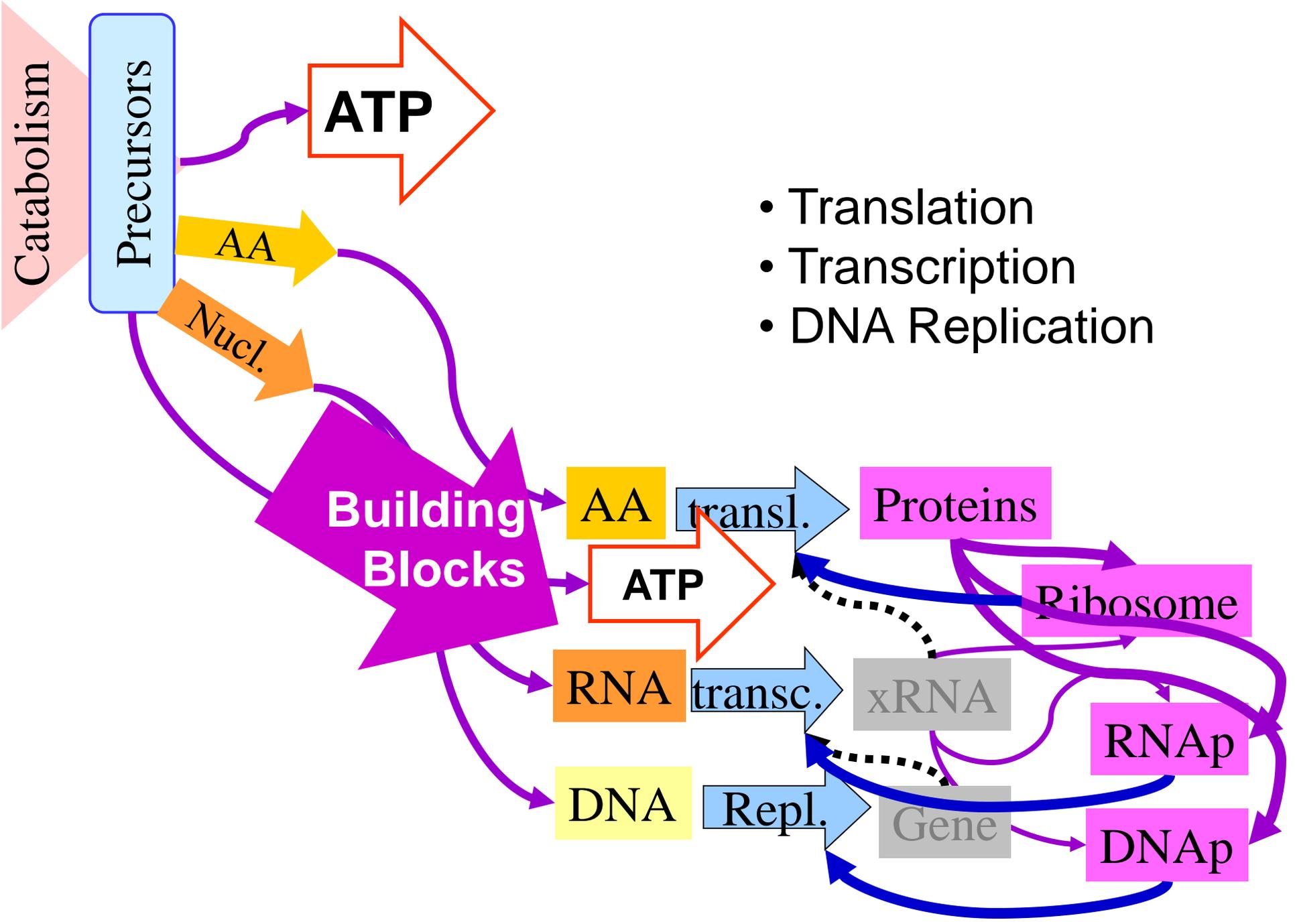
Huge Variety



Inside every cell



Translation: Amino acids polymerized into proteins



Inside every cell

